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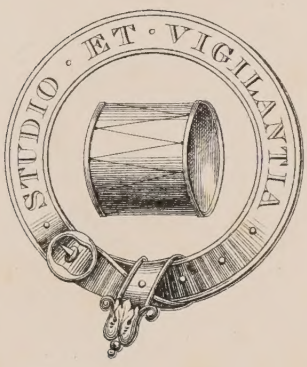

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Professor A. Mac Fadyen
With the Kind regards of the Authors

ON

CARBOHYDRATE METABOLISM

(A Course of Advanced Lectures in Physiology delivered at the University of London, May, 1905)

WITH AN

APPENDIX ON THE ASSIMILATION OF CARBOHYDRATE INTO PROTEID AND FAT

FOLLOWED BY

THE FUNDAMENTAL PRINCIPLES, AND THE TREATMENT, OF DIABETES DIALECTICALLY DISCUSSED

BY

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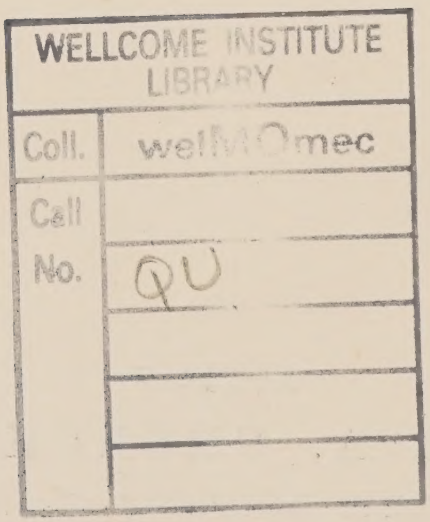

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PREFACE.

Carbohydrate is viewed in this volume from a twofold aspect—physiological and pathological. When physiological procedure is in operation, the carbohydrate principles of our food are dealt with in the system in a manner to be rendered applicable to utilisation, and, in passing to utilisation, they become lost sight of after being ingested. When, on the other hand, pathological instead of physiological procedure confronts us, carbohydrate matter fails to be placed in the requisite position to proceed to utilisation, and, in consequence thereof, simply traverses the system in the form of sugar to become discharged as such with the urinary water, the issue being diabetes. Pathology steps in on account of default in the fulfilment of the part that ought to have been carried out as a physiological proceeding. The two points of consideration being thus related, a knowledge of the physiological operations involved in carbohydrate metabolism constitutes a necessary preliminary to a right comprehension of the pathology of diabetes. Physiology is truly regarded as the handmaid of medicine, and nowhere does this position more strongly hold good than in connection with the matter before us.

This leads to an inquiry into the position in which the glycogenic doctrine stands being called for. Under this doctrine it is taught that our carbohydrate supply is transported in the form of free sugar through the circulatory system to the seat of utilisation in the tissues. Such a procedure in reality implies the production of glycosuria; for sugar, with its small molecular constitution, if allowed to reach the circulation, cannot be prevented from running off in a *pari passu* measure

with the urine. To be kept out of the urine, sugar must be kept out of the general circulation, and this, under natural circumstances, is effected by the occurrence of carbohydrate assimilation in accordance with the principles enunciated in this work.

As an outcome of the teaching of the glycogenic doctrine it is suggested that the transport of sugar through the circulatory system to the systemic capillaries for oxidation and force production constitutes a necessary phenomenon of life, and upon these premises it is argued that a supply of carbohydrate food is needed by the diabetic. In spite of the circulatory system being charged with a redundance of sugar from which pernicious effects are being produced, the supply of carbohydrate, with the attendant abnormal condition arising therefrom, is to be maintained. With the greatest confidence it can be affirmed that, as a matter of fact, no principle of action could be productive of more sinister results.

The glycogenic doctrine, then, stands far otherwise than in the position of a mere question of abstract science. No less an important matter than the principle of action to be put into force in the dietetic treatment of diabetes is at stake in connection with it. If physiology is to hold its right position, and to act as a guiding instead of a misleading factor in relation to medicine, the interests of medicine demand that the glycogenic doctrine should be abandoned. To satisfy the requirements of the case I consider it must be said that nothing short of a clean page is needed upon which the subject must be treated upon different lines from those hitherto adopted.

To Dr. Selous and Dr. Leslie Eastes I desire to tender my thanks for the assistance rendered by them in the preparation of the sections of the villi depicted in this work, and to Messrs. W. Watson & Sons for the care bestowed upon the production of the photomicrographic illustrations. To Dr. H. W. Bywaters I am indebted for the preparation of the index, and for much aid in carrying the work through the press.

35, Grosvenor Street, Grosvenor Square.
March, 1906.

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ON
CARBOHYDRATE METABOLISM.

THIS is a large and important subject, and one which takes us into the question of the series of operations occurring in the application of food, as a whole, to the purposes of life. The primary classification of the organic portion of food is into nitrogenous and non-nitrogenous. Avoiding descent into particulars, the nitrogenous may be spoken of under the head of proteid. The non-nitrogenous consists of fats and carbohydrates. There are these two distinct divisions to start with, but as we proceed we shall find that these become so intimately mixed up in their passage through the body as to lead to the consideration of the one necessarily bringing in that of the others.

The destination of food is the growth and renovation of the component parts of the body and the production of energy. For these purposes the actual seat of utilisation is within the protoplasmic or biogenic molecules constituting the basis of living matter. It is here where the active changes of life occur. Food elements on the one hand, and oxygen on the other, enter the large and highly complex molecules of which protoplasm is composed, and, through the play of changes ensuing, the phenomena of life are evoked. As an outcome of this proposition the food material has to reach these protoplasmic molecules and to traverse the circulatory system in doing so. In what precise manner the transit is carried out will have to engage our attention. The problem is mixed up with considerations of a complicated nature. Modern research shows that what has to be dealt with is something far otherwise than a simple passage of

nutrient chemical principles into the blood at the seat of absorption and their conveyance as such to the seat of utilisation in the tissues. The blood has an intermediate part to play, in connection with which, as I shall have to point out, there is evidence to show that living protoplasmic action is concerned.

The first stage for all kinds of food to pass through is that of preparation for absorption. Solid matter requires to be brought to the liquid state, and all nutrient principles to be placed in a condition to which the property of diffusibility belongs. This is effected by enzyme action, the enzymes being products of secretion of the digestive system adjusted by Nature to accomplish the purposes required to be fulfilled, and, as we shall see further on, being modified by the character of the demand existing so as to meet the wants arising from the particular kind of food supply.

Digestion is a necessary part of my subject in tracing the ingested food on to the disposal of it by utilisation. Something requires to be said upon the point, but I do not propose to dwell to any great extent upon it. The polysaccharides—starch and cellulose, the disaccharides—maltose, lactose, and saccharose, and the monosaccharides—dextrose, lævulose, and galactose, are the chief carbohydrates that have to be dealt with in connection with alimentation. Evidently in some of the lower animals an enzyme is provided that is capable of attacking and dissolving cellulose. In the human subject, however, it is doubtful if cellulose is to any material extent digested. Cytase is the name given to the enzyme that has been discovered for hydrolysing cellulose, but information with regard to it is in an incomplete state.

Starch may be spoken of as the most important carbohydrate entering into the constitution of our food. Whilst in the state of starch, it is an absolutely useless material on account of the resistance it offers to being absorbed. It readily yields, however, to the hydrolysing influence of the enzymes with which it is brought into contact, and thus is placed in a position to be susceptible of utilisation in the body. The saliva and pancreatic juice contain a diastatic ferment which possesses the power of carrying it through

dextrinoid stages into maltose as an end product. This is the limit of change effected by diastase. The action, however, has been found to be attended with the production of a little glucose, attributable, probably, to the presence of a minute amount of the glucose forming ferment to which the name of glucase is applied. In the intestinal mucous membrane an active glucose forming capacity exists, so that as a final issue, before absorption occurs, the hydrolysis of starch presumably proceeds to the end stage of enzymic transmutation, or, in other words, to the production of glucose.

Cane sugar or saccharose may be taken next to starch. This is a very soluble and diffusible principle, and therefore is in a position to pass with ease from the alimentary canal into the circulatory system. Did it pass, however, it would subsequently simply filter through the body and escape with the urine in an unutilised state. All experience goes to show that saccharose as such is not susceptible of application in the system. It remains untouched by the living protoplasm, and therefore cannot take part in the operations of life. Virtually holding the position of extraneous matter, it is dealt with by the system accordingly. It is most easily, however, placed in an altered state by enzyme action and thereby rendered serviceable.

Invertase is the name of the ferment that accomplishes this work, and its effect is to insert a molecule of water, and resolve the body into a molecule of dextrose and a molecule of lævulose. The small intestine is known to contain this enzyme. It is stated that the stomach does not. I have found, however,[1] that to a certain extent it does, and that introduced into the stomach when digestion is going on saccharose is pretty extensively converted into glucose. In the ruminant animal a modified state of things exists. The intestine possesses very little transformative energy—not more than is observed in the case of the stomach with animals generally. The inverting power is situated in the multiple stomach and is possessed by the paunch and many-plies to a much higher degree than by the reticulum and by

[1] *Physiology of the Carbohydrates*, 1894, p. 94.

the reed or true stomach. Thus, means exist through the provision of enzyme action in connection with the alimentary canal for placing ingested saccharose in a utilisable condition. These means must very efficiently fulfil their object, seeing that if saccharose were allowed to reach the circulation it would filter off as waste material with the urine, and it is not observed to do so. I have examined the portal blood after the experimental introduction of large amounts of saccharose into the stomach, and have obtained no evidence of its presence. By excessive feeding with cane sugar the urine may be rendered saccharine, but glucose is the kind of sugar found. In diabetes the cane sugar ingested escapes as glucose. Apart from the alimentary canal invertase does not exist. This is proved by the intravenous and subcutaneous injection of cane sugar being followed by no signs of the production of glucose. Both the blood and the urine are found to give evidence of the presence of cane sugar, but none of produced glucose.

Observation on the yeast organism teaches us exactly the same as we learn from what is observable in connection with the animal system. Cane sugar is of no use to the yeast cell; its protoplasm will not touch it for functional application. By the invertase, however, which the organism contains transformation into glucose is effected, and now the application occurs. The cane sugar molecule, it may be considered, is not of a nature to be susceptible of being anchored on by, and incorporated into, the protoplasmic molecules of the yeast, and as long as it remains in an unchanged state, it resists being influenced, just as it resists being touched when introduced into the circulatory system of an animal.

Lactose holds a similar position to cane sugar or saccharose, and, whilst existing as such, is not susceptible of protoplasmic utilisation. It is a disaccharide, and when hydrolysed, splits into a molecule of dextrose and a molecule of galactose. The enzyme that effects this change is called lactase. Knowledge regarding this enzyme has not been extensively worked out. Its chief seat appears to be the mucous membrane of the small intestine, and it may be

assumed that ingested lactose here undergoes transformation preparatory to absorption from the alimentary canal. As with saccharose, it is noticeable that lactose reaching the alimentary canal of a diabetic passes off as glucose in the urine. Evidence is here afforded of the actual occurrence of the change within the system.

It thus appears that each of the carbohydrates that has been spoken of requires to undergo full hydrolysis into a monosaccharide to become fit for utilisation. Starch evidently does not stop at the disaccharide state of maltose, but, like its congeners saccharose and lactose, passes on into the monosaccharide form.

It is seen that by enzyme action the non-utilisable carbohydrates are put into a state to be susceptible of appropriation by living protoplasm, and adaptability in this respect is traceable to the particular requirements existing. The adaptive power of Nature is a matter of common observation in very diverse directions. When the food is not of the character to require the action of a diastatic ferment none is provided. The salivary glands of the infant are not developed at the first period after birth, when milk constitutes the natural food. At this time, also, the pancreatic juice has no power of digesting starch.

Bainbridge[1] has recently investigated, with respect to lactase, the adaptation of the pancreatic secretion to the nature of the food. Independently of the nature of the food, lactase is always present in the mucous membrane of the small intestine, but in the case of the pancreas its production is dependent upon whether the animal is being fed on milk or not. In biscuit-fed dogs neither the pancreas nor its secretion contains any lactase. In milk-fed dogs, on the other hand, after the continuance of the feeding for two or three weeks, lactase is to be discovered in both the pancreas and its secretion.

The mechanism of this adaptiveness has been worked out and found to depend on the influence of the ingested lactose on the mucous membrane of the small intestine. Through

[1] *Journal of Physiology*, vol. xxxi, p. 98, 1904.

the interaction occurring a "tangible something" becomes developed which reaches the blood-stream, and, by it, is carried to the pancreas, where it gives rise to the production of lactase for assisting in the digestion of the lactose that is entering into the composition of the food. This "tangible something," which acts upon the secreting cells of the pancreas in the manner that has been mentioned, is susceptible of being extracted from the intestinal mucous membrane and produces its effect on being artificially injected into the system. For example, observation has shown that the subcutaneous injection of the extract obtained from the intestine of a milk-fed dog leads to the production of lactase, whilst from the extract obtained from a biscuit-fed dog no effect is produced.

The object of digestion is the preparation of food for absorption, and the several changes in carbohydrate matter that have been referred to, fall within the scope of this process. Ideas regarding what is wanted for placing nutrient matter in a suitable position for application in the system have in recent times undergone great development. In this remark I have in view the molecular conformation that is needed to be provided to permit of entry into living protoplasm, and, thence, of taking part in the metabolic changes occurring, a point upon which I shall have much to say later. Formerly it was considered sufficient to regard digestion as bringing the food into a liquid and diffusible state, so as to be rendered fit for the occurrence of absorption in compliance, as the idea ran, with the physical laws of osmosis.

It is interesting to look back upon the crude state of knowledge of organic chemistry that existed when the study of the physiological relations of sugar was first started. But little was known about precise methods of preparation for analysis, and analytical procedure had none of the delicacy and precision with which it is invested at the present day. Instead of any actual quantitative determination being made of the sugar present in the blood of different parts of the circulation, the estimation was based simply upon the character of the copper test reaction that was obtained.

Regarded as a heat producer, the sugar molecule was

supposed to undergo direct oxidation in the manner that combustion is carried on in carbonaceous matter around us, and, originally, the lungs were looked upon as constituting the seat of combustion, on account of arterial blood, owing to the mode of experimenting pursued, being regarded as containing, to a pronounced extent, less sugar than that of the right ventricle. My first experiments upon the physiology of sugar were directed to ascertaining if the destruction of sugar supposed to take place during the transit of blood through the lungs of the living animal would do so during transit through excised lungs subjected to inflation in imitation of respiration. For obtaining the blood for injection I resorted to catheterism of the right ventricle of another animal, and this led up to my finding that right ventricular blood during life was not charged with sugar in the manner that had previously been supposed from the condition observed when collected, as had hitherto been done, after the destruction of life. Seeing that there was this disparity between right ventricular blood collected during life, and that obtained after death without the adoption of the precautions now known to be necessary to escape from the effects of post-mortem alteration, it occurred to me that investigation ought rightly to be extended to the liver to ascertain the position in which this organ might be found to stand in relation to ante- and post-mortem conditions. I must confess I did not at starting expect to obtain a result different from what had hitherto been met with. On experimenting, however, in a manner to obtain a representation of the condition of the liver at the moment of death, it was found that there was no more evidence afforded of the presence of sugar than is derivable from the examination of other constituents of the body. Thus, in the case of both right ventricular blood and the liver, experiment showed, when conducted in such a way as not to allow time to elapse for the influence of post-mortem change to be exerted, that the conclusions which had been previously formed, and which had led to the establishment of the glycogenic doctrine, were based upon a faulty foundation.

The glycogenic doctrine also included the destruction of

the sugar alleged to be produced by the liver and poured into the circulation through the hepatic veins. After the lungs were no longer looked upon as the seat of destruction, the systemic capillaries were assigned as constituting the position in which combustion of sugar—for it has been customary to speak of it as a process of this simple nature—occurred. In support of this view experimental evidence was advanced representing arterial blood as containing considerably more sugar than venous. This, as history shows, I could not find to be the case, a large number of carefully conducted experiments having resulted in revealing no real difference as regards amount of sugar between the two kinds of blood. Modern investigators have supplied confirmatory testimony, and even Lépine, one of the foremost and staunchest supporters of the glycogenic doctrine, has joined in giving expression to a similar conclusion. In the *Comptes Rendus* of the Académie des Sciences for the *séance* of November 2nd, 1903, Lépine and Boulud, after a reference to what they stated in a previous communication, say that very often there exists more sugar in the blood of the carotid artery than in that of the right ventricle, and then proceed to affirm that in some cases at least more sugar is found in venous than in arterial blood. An example cited gives 0·80 per 1000 for the arterial and 0·86 for the venous. What a change of front to be assumed by the French school! An experimental record supplied in former days by Bernard showed a diminution by half of the sugar in arterial blood during transit through the capillaries to the veins, the actual figures belonging to the experiment in question being 1·450 per 1000 for the arterial and 0·730 for the venous blood. With the knowledge we now possess it may be unreservedly asserted that experimental fallacy must have here existed. If, in accordance with the above-mentioned statement of Lépine, the right ventricular blood may contain less sugar than the arterial and the blood in the arteries less sugar than that in the veins, what, it may be asked, becomes of the glycogenic theory in connection with which it has been all along contended that exactly the reverse order of things has to be dealt with?

Although the experimental evidence showing the fallacious ground on which the glycogenic doctrine has been built seems to be pretty generally accepted, a lingering idea appears to prevail that the sugar derived from the food passes as such through the circulation to the tissues, where it serves for utilisation. Undoubtedly the carbohydrate must reach the tissues, but the great point in connection with the matter is as to the form under which the conveyance takes place. I will proceed to deal with the question, and I think it will be seen that it is quite incompatible with the circumstances existing that a small molecular body like sugar can constitute the medium for the transmission of food carbohydrate from the seat of absorption to that of utilisation.

Everything points to the impossibility of keeping the sugar molecule within the limits of the circulating current. When circulating through the kidney it cannot be prevented from escaping like other small molecular bodies and making its appearance in the urine. Impermeability of the kidney to sugar has been spoken of and suggested as a means of permitting sugar to reach the tissues without running off with the urine. I consider it may be confidently asserted that this suggestion has not a vestige of real support. No matter in what way sugar reaches the circulation, it, in proportion to the extent that it does so, shows itself in the urine. The urine thus becomes an indicator of the state of the contents of the circulation as far as sugar is concerned.

Let us pause for a moment and view this matter by reference to our present-day notions of the mechanism of renal secretion. From the method of experimenting that has during the past few years been adopted, our knowledge upon this point has been deprived of much of the speculative character that formerly belonged to it. The first event may be pretty safely concluded to be a simple filtration through the Malpighian tuft into Bowman's capsule. In this filtration the water of the blood-plasma carries with it, proportionately to their presence, the crystalloids or small molecular bodies—urea, salts, sugar, etc.—that may exist in it, just as happens when water holding in solution various crystalloidal substances

is thrown upon an ordinary filter. It is impossible to conceive that any differentiation could occur and that the sugar molecules could be held back whilst molecules of an allied nature should be allowed to pass. Pressure is at work in connection with the filtration, so that the fluid is driven through the walls of the glomerular capillaries. The next event is the passage of the filtrate along the uriniferous tubules, where it becomes altered in character and transformed into urine by the agency of the tubular epithelial cells with which it is brought into contact. These are secreting and absorbing cells. They have been likened in their action on the fluid in transit through the tubule to the cells lining the intestinal canal (Cushny). The rate of transit plays an important part. When, as under high blood-pressure and renal arterial dilatation, the filtrate is excessive, it may travel through the tubule with a velocity that permits but little alteration to occur, but when the transit is slow, evidence of selective re-absorption is presented. Water is re-absorbed freely, and, as is noticeable in the intestine, sodium chloride is more freely taken up by the cells than sodium sulphate and sodium phosphate. The cells apparently, like other cells of the body, show no disposition to touch urea. Sugar, presumably, is taken up to some extent, and, further, a modifying effect is in some way or other produced, inasmuch as that which passes on with the urine, as will be seen later, has a lower cupric oxide reducing power than the sugar of the blood. Either an influence is exerted by the cells on the sugar, or, it might be, the glucose is taken up by the cells in preference to the other sugars belonging to the blood.

I will now proceed to illustrate the relationship existing between blood and urine with reference to sugar by the evidence derivable from its experimental introduction into the system. A little time back I undertook a series of experiments on the intravenous and subcutaneous injections of different sugars. The results were published in the *Journal of Physiology*, vol. xxiv, 1899, the title of the paper being "An Inquiry into the Effects on the Blood and Urine of the Intravenous and Subcutaneous Injection of Various Carbohydrates standing in Relation to Animal Life." The sugars

employed consisted of the disaccharides—saccharose, maltose, and lactose, and the monosaccharides—dextrose, lævulose, and galactose. Upwards of 200 observations are included in the paper.

The experiments were conducted on rabbits, and for the intravenous injection the vein which occupies quite a superficial position and runs close against the outer edge of the thin part of the ear was selected. Into this vessel it is easy to pass a subcutaneous injection needle without apparent consciousness by the animal, and, therefore, without needing the exercise of restraint beyond that of holding in a steady position with the hands of an assistant. The sugar solution was run in from a graduated burette, to the top of which was affixed an indiarubber bag with inflator to produce the requisite pressure. From 25 to 30 c.c. per minute was the rate at which it was usually introduced. Attention had to be given to secure that the blood was collected without the opportunity being afforded for post-mortem change to occur. The method adopted was to kill by pithing, and instantly afterwards to cut into the chest with scissors and snip across the heart, from which the blood, after turning the animal over, was collected in a basin. Measured by a chronograph, the time occupied by pithing and the collection of the blood was upon an average about 15 seconds. The alcoholic method of extracting the sugar from the blood was adopted so as to permit of the nature of the sugar present being ascertained by taking the cupric oxide reducing power before and after hydrolysis by means of boiling with a mineral acid. The ammoniated cupric test (Pavy), which, I think I may say, is admitted to constitute an exceedingly delicate and at the same time trustworthy test, was used for effecting the determinations. The symbol K is employed to represent the cupric oxide reducing power of the sugar or sugars present as compared with that of glucose expressed as 100.

I have already said that the urine is an indicator of the state of the blood with reference to sugar. The definite small quantity of sugar in all circumstances present as a standard constituent of the blood is represented in the urine by an

equally definite and constant presence of sugar. At one time it was a disputed point as to whether sugar existed in healthy urine. There may be those who remember that a controversy, with some warmth introduced into it, was some years ago carried on in the pages of the *Lancet*. I was one of the disputants and contended on the affirmative side, grounding my position upon the crucial evidence I had obtained of reaction with the fermentation test applied to the product collected from large quantities of urine through the medium of lead and ammonia precipitation. Since this time Emil Fischer's phenyl-hydrazin test has set the matter completely at rest. An osazone is always readily obtainable from the extracted sugar derived from a moderate quantity of urine, and it is even possible for crystals to be procured by direct procedure from the urine in its ordinary state by persons who are skilful in the application of the process. The actual quantity of sugar present is easily revealed by means of the ammoniated cupric test. Whilst Fehling's solution gives no visible reaction, a distinctly appreciable amount is shown to be present by the ammoniated cupric test, and where Fehling's solution gives, as is often seen in concentrated urine, what may be considered as an approach to a reaction, somewhat notably high figures, certainly in view of the fact that normal urine is being dealt with, may be obtained. We speak of urine as being free from sugar when no perceptible reaction is given by Fehling's solution, but all the time a certain amount of sugar, corresponding with that existing in the blood, is present. It is the nitrogenous constituents of the urine that conceal the reaction, and they do so by giving rise to the development of ammonia, which prevents the occurrence of a deposit of suboxide. No doubt these circumstances have had something to do with establishing the idea of renal impermeability to sugar, and the idea arising out of it that sugar can be present in the blood without passing off with the urine.

It will be convenient to state here that neither in the case of healthy urine nor in that of blood does the sugar actually consist entirely of glucose. It is customary to speak of glucose as the kind of sugar belonging to the blood. Observa-

tion shows that this does not represent the precise truth. Alike by the cupric oxide reducing power indicated before and after hydrolysis, and the osazone crystals obtainable, it is demonstrable that sugar of other nature than glucose is present. A communication on this point is to be found in the *Journal of Physiology*, vol. xxvi, 1901 ("On the Nature of the Sugar Present in Normal Blood, Urine, and Muscle," by Pavy and Siau), in which the matter is fully dealt with. Extracting the sugar with alcohol, which would exclude glycogen and the lowest dextrins, the product obtained from blood, urine, and muscle, was in each case found to possess a cupric oxide reducing power considerably below that of glucose, and with phenyl-hydrazin gave an osazone corresponding both in crystalline form and melting point with glucosazone, and another corresponding with the osazone derivable from what has been designated by Fischer and others isomaltose. Probably in reality a mixture of sugars and higher dextrins exists presenting a condition that will serve to account for the very varying degrees of cupric oxide reducing power that may be met with.

Before referring to the injection of sugar experiments it is advisable that a representation should be given of the state existing in connection with normal blood and urine. The following observations serve this purpose :

Normal Cardiac Blood.

Animal.	Sugar per 1000. Before hydrolysis.	After hydrolysis.	K.
Rabbit	0·997	1·407	71
,,	0·993	1·255	79
,,	0·967	1·261	74
,,	0·939	1·458	64
,,	1·261	1·740	72
,,	1·039	1·558	67
,,	1·316	1·790	73
,,	1·170	1·520	77
,,	0·992	1·325	75
,,	1·116	1·700	65
,,	1·088	1·300	83
,,	1·200	1·630	75
Mean	1·089	1·495	73

Animal.	Sugar per 1000. Before hydrolysis.	After hydrolysis.	K.
Cat . . .	0·986	1·136	86
„ . . .	1·000	1·190	84
„ . . .	0·883	0·975	90
„ . . .	0·712	1·030	69
„ . . .	1·026	1·409	72
„ . . .	0·684	1·104	62
Mean . . .	0·880	1·140	77
Dog . . .	0·860	1·300	66
Horse . . .	1·160	1·550	75

All the above instances apply to ordinary conditions as regards food, and it is seen that in the vegetable feeder the figures stand a little higher, taken as a whole, than in the animal feeder, but there is not any large difference noticeable, and, looked at individually, irregularity is perceptible. To ascertain the condition existing apart from the influence of food, animals were taken after fasting for a period sufficient to occasion not far short of a disappearance of glycogen from the liver. The following were the results given:

Cardiac Blood of Fasting Animals.

Animal.	Sugar per 1000. Before hydrolysis.	After hydrolysis.	K.
Rabbit . . .	1·28	1·73	73
„ . . .	1·49	2·13	70
„ . . .	1·46	2·06	70
„ . . .	0·93	1·17	79
„ . . .	1·04	1·44	70
„ . . .	1·06	1·34	79
Mean . . .	1·21	1·64	74
Cat . . .	1·27	1·33	95
„ . . .	0·94	0·98	96
Mean . . .	1·10	1·15	96

Normal Urine.

Animal.	Sugar per 1000. Before hydrolysis.	After hydrolysis.	K.
Rabbit	3·33	6·60	50
„	5·89	11·92	49
„	0·68	1·80	38
„	1·06	2·38	44
„	2·40	5·36	46
„	3·70	7·90	42
„	8·80	16·54	53
„	4·89	9·06	54
„	2·98	6·14	48
„	1·86	3·21	57
„	2·33	4·03	57
„	4·00	7·00	57
„	4·66	8·75	53
„	4·30	7·24	59
„	6·08	10·32	58
„	2·22	4·27	52
Mean	3·69	7·03	52
Cat	1·78	3·76	47
„	1·73	3·36	51
„	3·02	7·75	39
„	2·27	5·41	42
„	2·10	4·64	45
„	2·17	6·00	36
„	3·31	4·54	73
„	1·38	3·21	43
„	4·90	9·00	53
„	3·60	7·99	45
„	4·08	8·96	46
„	2·73	5·86	47
Mean	2·75	5·87	47
Dog	4·07	6·36	64
Horse	4·41	7·40	60
Human subject	0·91	1·89	48
„ „	2·87	5·05	57
„ „	4·07	6·25	65
„ „	4·41	6·90	64
„ „	3·57	5·40	66
„ „	2·55	4·25	60
„ „	4·88	6·90	71

	Sugar per 1000.		
	Before hydrolysis.	After hydrolysis.	K.
Human subject . .	2·83	4·54	62
„ „ . .	2·27	4·05	56
„ „ . .	1·66	3·41	46
„ „ . .	2·12	4·28	50
„ „ . .	1·35	2·63	51
Mean . . .	2·79	4·63	60

I have previously directed attention to the condition of the blood taken after a period of fasting. I will likewise do so for the urine. The specimens were derived from the same set of observations.

Urine of Fasting Animals.

	Sugar per 1000.		
Animal.	Before hydrolysis.	After hydrolysis.	K.
Rabbit . . .	0·68	1·80	38
„ . . .	1·06	2·38	44
„ . . .	2·40	5·36	46
„ . . .	3·70	7·90	42
„ . . .	3·30	6·60	50
Mean . . .	2·23	4·80	46
Cat	4·90	9·00	53
„	3·60	7·99	45
„	4·08	8·96	46
Mean . . .	4·19	8·65	48

Looking at these observations, it is noticeable in every instance that the cupric oxide reducing power after treatment with the mineral acid is conspicuously higher than that before. It is further noticeable that K runs in a decidedly lower range of figures in the case of the urine than in that of the blood. This I consider has a bearing upon the direction taken by sugar within the animal system, and I shall have occasion to comment upon it later. As regards the genesis of the increase of cupric oxide reducing power by the agency of the acid, it is only, I believe it may be said, by hydrolysis of a carbohydrate, or by cleavage of a glucoside, that the phenomenon can be accounted for.

It follows from what has preceded that not only does healthy urine contain a definite amount of sugar, but that the sugar present is not to be regarded as consisting simply or even mainly of glucose. Uric acid and creatinine are cupric oxide reducing bodies, and we must not be oblivious of the fact that they must contribute something towards the production of the cupric oxide reducing result obtained. They are not present, however, to a sufficient extent to answer for much in this direction, and they can have nothing whatever to do with the increased figures obtained after hydrolysis by treatment with the acid. As a source, indeed, for the production of these increased figures we can only look, as I have stated, to the presence of carbohydrate matter of lower cupric oxide reducing power than glucose or to the liberation of sugar from a glucoside. The phenyl-hydrazin reaction shows that a maltose type of sugar is present, but to account for the results frequently seen to have been obtained, the presence likewise of much lower cupric oxide reducing carbohydrate matter than this is needed. That glycogen or animal gum cannot be advanced as the source of explanation I have found is rendered evident by the agency of alcohol in which these principles are insoluble. Urine has been evaporated almost to complete dryness and then extracted with alcohol. The filtered alcoholic extract after evaporation and subjection to the acid treatment has given the same character of result as the urine in its ordinary state.

The amount of sugar that may be found is seen to be very variable. The degree of concentration of the urine seems to be the main factor in connection with this point. It is a matter of common observation to find, in applying the ammoniated cupric test to ordinary urine, that it is specially in high specific gravity specimens that the maximum amounts are met with. Indeed, with very high specific gravity specimens it is not an uncommon event for Fehling's solution to give a greater or less degree of reaction, and instances have from time to time occurred in which the result has been interpreted as indicating the existence of an abnormal glycosuria. The medical practitioner, in fact, requires to be

on his guard not to be misled by the result obtained on testing a high specific gravity urine. I might adduce many examples in illustration of what I have stated about the relation of the sugar indication to specific gravity. I will be content with the following. The first two specimens in the foregoing list of examples from the human subject were obtained from the same individual and were passed at periods within a few hours of each other. One was of specific gravity 1008 with the sugar indication mentioned of 0·91 per 1000 before hydrolysis, and 1·89 per 1000 after. The other had a specific gravity of 1024 with a sugar indication of 2·87 per 1000 before hydrolysis, and 5·05 per 1000 after. In an instance where I took the sugar indication of urine of specific gravity 1002 it was found to stand at 0·34 per 1000.

Not only in all urines is there seen to be a decided amount of sugar present, but in some, which must nevertheless be regarded as falling within the normal category, the amount reaches a point that would hardly have been looked for under the notions that have hitherto been entertained. In the case of one of the rabbits, for instance, the figures stood at 8·80 per 1000 before hydrolysis and 16·54 per 1000 after, which gives a K of 53. The K is normal, and the condition simply represents an undue proportion of normal sugar indication such as might be produced as a result of concentration. It is the elimination of glucose which is characteristic of abnormal glycosuria, and if the high sugar indication had been due to this, K would have stood much higher than it did. The effect of adding glucose to healthy urine is theoretically and practically to bring the figures obtained before and after hydrolysis nearer to each other, and as the quantity added advances, the effect of the lower cupric oxide reducing sugars that happen to be present becomes more and more thrown into the shade until it ceases to be perceptible. Thus K serves to point out, when undue sugar indication exists, whether it is the result of a heightened normal state or an abnormal output of glucose.

I have stated that it is the abnormal output of glucose that belongs to glycosuria as a morbid condition. As the result of

treatment of the case, the urine may be brought to a natural state and give no reaction with Fehling's solution. It will be understood, however, that it contains sugar in small amount, as happens with healthy urine. In these cases a little dietetic deviation readily affects the urine and may cause it to give more or less change indicative of sugar on being boiled with Fehling's solution. The sugar may not be greater in amount than may be sometimes met with in concentrated urine from the healthy person, but on taking the cupric oxide reducing power before and after hydrolysis the resulting K is found to stand higher. The following are a few instances illustrative of this point.

Urine from mild Glycosurics with associated Output of a slight Amount of Sugar.

Sugar per 1000.		
Before hydrolysis.	After hydrolysis.	K.
4·31	5·05	71
5·81	7·20	80
7·35	9·09	81
7·81	9·87	79
6·66	7·48	88
6·25	7·80	80
6·58	8·92	74
4·63	6·94	67
7·69	8·72	88
5·00	6·30	79

Having dealt with the normal state of blood and urine in relation to sugar, I will next proceed to consider the condition observed after the direct introduction of sugar into the system by intravenous injection. When a large quantity is introduced in this way it literally runs out through the kidney as it is injected into the vein. It is almost incomprehensible the rapidity with which the sugar in these circumstances reaches the urine. It passes through the kidney almost like running through an ordinary filter. With the injection of four grms. per kilo. body-weight sugar was discoverable in quantity in the urine instantly after the

completion of the injection. Ordinarily the injection occupied somewhere about 60 seconds and the subsequent instantaneous pithing and collection of the right ventricular blood another 15 seconds. It would be within these limited periods of time that the escape of sugar could be taking place from the kidney, and yet it was found after the employment of saccharose that the urine collected from the bladder contained in one instance as much as 64, and in another 74, per 1000 of this sugar. Looking at the lengthy route to be traversed in passing through the kidney, the question suggests itself whether it might not pass direct into the urine contained in the bladder by osmosis from the vessels of the organ, but presumably the result is not to be accounted for in this way. With dextrose dealt with in a similar manner the escape was a little less active, the two highest instances of figures given being 39 and 47 per 1000.

A strikingly noticeable effect of the injection of sugar in the quantity named when the animals were not killed immediately was a greatly increased flow of urine. The intensity of the diuresis was such that in the collection of the urine as a part of the experiment it was found, in order to avoid loss from spontaneous escape, that considerable vigilance was required to be exercised to keep pace with the activity of secretion. The method of collection was by pressure over the bladder with the thumb.

The determinations made of the amount of sugar present in the blood in the several injection experiments showed a variation for the different sugars, but comparative uniformity was observable for each kind of sugar. On the sugar reaching the circulation two influences can be mentioned that would immediately come into operation and produce their modifying effect. Water is drawn by osmosis from the tissues and the blood becomes thereby more or less extensively diluted. This, it may be stated, has been found experimentally to occur. There must also be diffusion of sugar from the blood into the tissues. Our knowledge does not permit us to speak of any other tangible physical influence that would come into play.

Intravenous Injection of 4 Grms. per Kilo. Body Weight.

The following are the respective amounts of the different sugars found in the blood after the injection of 4 grms. per kilo. The sugar in each case is reckoned as glucose and expressed in parts per 1000.

Blood Collected from Animal Killed Instantly after the Injection.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
24·26	20·00	17·32	13·93	14·94	14·83
24·52	17·90	18·73	11·11	17·00	14·20
21·66	—	—	11·11	17·30	14·94
21·21	—	—	—	14·58	15·48

Blood Collected from Animal Killed 5 Minutes after the Injection.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
13·04	10·30	12·05	10·37	10·56	10·20
15·80	10·62	10·04	—	10·56	10·72
—	—	—	—	9·88	—

Blood Collected from Animal Killed 15 Minutes after the Injection.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
12·10	8·50	8·66	8·33	7·22	7·35
12·06	10·00	7·43	—	7·50	8·17
11·66	—	—	—	7·37	8·59
—	—	—	—	—	8·59

Reviewing these figures, the disparity that existed in the instantaneously collected bloods has in great measure disappeared in those collected after the lapse of 15 minutes. In the former instance the disaccharides stand away from the monosaccharides in the larger amount of sugar found, and conspicuously is this the case for saccharose. At the end of 15 minutes, however, with the exception of saccharose, which still stands to some extent with higher figures than the rest, the sugar has fallen to a pretty uniform amount.

I will now give attention to the experiments in which one grm. of sugar per kilo. was injected, and it will be instructive

to view the results for both blood and urine set out in tabular form:

Intravenous Injection of 1 Grm. per Kilo. Body Weight.

Blood Collected Instantly.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
6·53	6·12	6·43	6·14	6·48	6·53
5·54	—	—	—	—	5·30
—	—	—	—	—	6·53

A striking uniformity is here noticeable for all the sugars.

Blood Collected at the end of 5 Minutes.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
4·90	4·34	3·63	3·39	3·92	4·22
4·37	—	—	—	—	—

Blood Collected at the end of 15 Minutes.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
3·60	3·81	3·51	2·66	2·57	2·32
3·22	—	—	—	—	3·14

Blood Collected at the end of 60 Minutes.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
1·88	2·33	1·59	1·66	1·29	1·42
1·97	2·91	2·05	1·79	1·49	1·59
—	1·75	1·70	1·66	1·66	1·50
—	—	—	1·73	1·41	1·51
—	—	—	1·79	1·37	1·55
—	—	—	—	1·60	1·12
—	—	—	—	—	1·38
—	—	—	—	—	1·28
—	—	—	—	—	0·70
—	—	—	—	—	1·22
—	—	—	—	—	1·31
—	—	—	—	—	1·41
Mean: 1·92	2·33	1·78	1·72	1·44	1·33

URINE.

Sugar, expressed as Glucose, Eliminated in One Hour after the Intravenous Injection of One Grm. per Kilo. Body Weight of the Undermentioned Sugars. The Figures represent Percentages of the Amounts Injected.

Saccharose.	Lactose.	Maltose.	Galactose.	Lævulose.	Dextrose.
80·4	51·9	56·8	31·7	19·7	12·8
82·8	45·1	56·3	38·6	28·6	9·2
80·0	49·1	56·5	31·7	15·6	2·8
—	—	—	19·6	19·8	11·7
—	—	—	23·1	19·5	28·1
—	—	—	—	22·7	15·4
—	—	—	—	—	19·2
—	—	—	—	—	17·0
—	—	—	—	—	10·2
—	—	—	—	—	11·3
—	—	—	—	—	18·4
—	—	—	—	—	31·5
Mean: 81·0	48·7	56·5	28·9	20·9	15·6

Thus it is seen, reading from the mean of the results, that 81 per cent. of the saccharose injected ran off with the urine in the space of an hour, 48·7 per cent. of the lactose, and so on for the other sugars. The results tally with the information given by the assemblage of experiments already dealt with. The saccharose molecule does not seem, if allowed to reach the circulation as such, to be susceptible of being touched by the system and thereby passes off into the urine in an unchanged state. Lactose and maltose to some extent correspond, but it looks as though they were partially put into a position to proceed to utilisation. With considerably more force does this remark apply to the monosaccharides, the elimination of these having been upon a much more limited scale. Of the three, the least extent of elimination occurred with dextrose and the highest with galactose. Lævulose stood not far from midway between the two. It is unassimilated or untouched molecules that escape with the urine. Those which pass into the assimilated state are placed

in a position to be removed from liability to pass off with the urine.

Intravenous Injection of 0·250 *Grm. per Kilo Body Weight.*

A further set of experiments was performed with the employment of a quarter of a grm. per kilo., which means $\frac{1}{4000}$th of the body weight. In this series only saccharose and dextrose were made use of.

Saccharose.

Intravenous Injection of 0·250 *Grm. of Saccharose per Kilo.*

	Sugar as glucose in blood per 1000.	Sugar as glucose in urine per 1000.
Killed instantly . . .	2·550	7·20
Killed at end of 5 minutes . .	1·973	14·80
Killed at end of 15 minutes . .	2·226	68·00

Dextrose.

Where large amounts of dextrose are injected the sugar met with in both blood and urine gives the appearance of consisting of glucose. The quantity of unchanged dextrose is such as to swamp the sugar of a lower cupric oxide reducing nature that may be present. I therefore have not considered it necessary previously to give more than one set of figures, namely, those representing the sugar in the fully hydrolysed state. In the case, however, where small amounts of sugar are employed, it is susceptible of being seen that some of it is changed by the system into a lower cupric oxide reducing body. On this account I consider it will be instructive to give, both for the blood and the urine, the figures obtained before and after hydrolysis.

Intravenous Injection of 0·250 *Grm. of Dextrose per Kilo.*

	Blood per 1000.			Urine per 1000.		
	Before hydrolysis.	After hydrolysis.	K.	Before hydrolysis.	After hydrolysis.	K.
Killed instantly . .	2·400	2·660	90	—	—	—
Killed at end of 5 minutes .	2·333	2·910	80	5·44	9·80	55
Killed at end of 15 minutes	1·430	2·040	70	4·90	10·50	46
Killed at end of 60 minutes	1·226	1·838	66	12·56	18·20	69
„ „ „	1·332	1·815	71	7·30	14·20	51
„ „ „	1·458	1·913	76	8·53	17·68	48
„ „ „	1·333	1·822	73	2·28	5·67	40
„ „ „	1·372	1·866	74	7·56	13·32	56

These results, following the intravenous injection of a quarter of a grm. per kilo. of saccharose and dextrose, show that as regards the blood there is not much difference observable in the amount of sugar constituent. As regards the urine, however, evidence is given of the disposition of saccharose to pass out of the system to an extent altogether beyond that observable for dextrose. It is quite in accord with what might be expected from all that has preceded that saccharose should be thrown out in the manner noticeable from the system, but notwithstanding the smallness of the quantity introduced, distinct signs are given in the case of dextrose also of a certain amount of escape in an unutilised state. Even at the end of an hour the blood had not regained its normal condition in relation to its sugar constituent, and with respect to the urine the figures give evidence of standing at a higher range than normal. The cupric oxide reducing power of the carbohydrate present, represented by K, is in accord with the usual order, and shows the influence exerted within the system in carrying carbohydrate to a lower cupric oxide reducing state. After the lapse of fifteen minutes K is observed to stand at the usual point noticeable for blood taken under ordinary conditions. For the urine K stands in its customary position at a considerably lower point than that for the blood.

Subcutaneous Injection.

I will now proceed to the consideration of the experiments in which the several sugars were injected subcutaneously instead of intravenously. The difference in the circumstances that presents itself will be readily realised. Introduced into the subcutaneous tissue the sugar solution is dispersed amongst the living structural elements of the areolar tissue and thence becomes only gradually absorbed. It is difficult to estimate how long it would take for complete absorption to occur, but in some of the experiments when the animal was killed two hours after the injection it was found that a watery condition of the tissue at the seat of injection existed, and that evidence of the presence of sugar was obtainable. To promote activity of absorption the part was well kneaded after the injection, so as to secure dispersal of the fluid. The bladder was emptied in the usual manner by pressure with the thumb before the injection. To escape as far as practicable from loss of urine, the first collection was made at the end of an hour. The plan, however, was not always successful, and in the table that has been framed loss of urine in circumstances that permitted of estimation is represented by an attached ? and by + where the loss could not be estimated.

Subcutaneous Injection of One Grm. per Kilo. Body Weight in 10 per cent. Solution. Animal Killed Two Hours afterwards.

In this table saccharose and lactose are seen to comport themselves in the same manner as after intravenous injection. Allowance must be made for the circumstance that absorption has to occur before they can reach the circulation and thence the urine. Allowing for this, the results point to their not being touched by the system but simply transmitted through it as so much extraneous matter. Galactose, lævulose, and dextrose evidently stand in a different position. In some instances the urine contained a highish percentage of sugar but in others little or no effect was observable. It looks as

Sugar employed.	Blood.			Urine.			
	Before hydrolysis. Per 1000.	After hydrolysis. Per 1000.	K.	Before hydrolysis Per 1000.	After hydrolysis. Per 1000.	K.	Sugar eliminated in relation to sugar injected. Per cent.
Saccharose	0·933	1·770	—	0·46	24·0	—	56
	0·793	1·400	—	4·40	253·6	—	59
	0·823	1·530	—	1·00	53·6	—	48
Lactose	1·333	1·831	72	61·18	122·36	50	41·6
	1·354	1·771	76	33·54	63·02	53	59·7
	1·444	1·999	72	63·00	134·20	46	23·5
	1·547	2·166	71	45·20	86·66	52	61·9
Maltose	1·761	2·978	59	2·80	6·41	43	7·4
	2·121	3·256	65	15·50	25·92	60	10·4
	2·021	3·456	58	7·00	13·71	51	8·5 ?
	1·547	2·363	65	28·10	35·44	78	10·7
	1·694	2·189	77	2·73	6·04	45	1·3
	2·039	2·427	85	7·06	16·51	42	3·8
Galactose	1·421	1·625	87	40·00	40·00	100	15·5
	1·333	1·666	80	17·33	17·33	100	24·0 ?
	1·468	1·805	81	6·58	6·84	96	13·1
Lævulose	1·390	1·430	97	13·07	—	—	7·0
	0·930	0·940	98	41·50	—	—	8·2
	1·310	1·450	90	8·50	—	—	8·1
Dextrose.	1·212	1·555	78	2·02	5·32	39	6·4
	1·416	1·961	73	9·07	14·20	64	2·5
	1·414	1·687	83	11·20	22·40	50	9·6
	1·371	2·050	67	16·30	22·80	71	2·7
	1·333	1·866	71	3·50	8·62	40	6·3 ?
	1·465	1·875	77	13·60	24·00	56	3·1
	1·238	1·625	76	7·88	18·56	42	4·8 +
	1·274	1·673	76	8·12	17·66	46	2·5
	1·020	1·238	82	1·62	5·29	30	6·4 ?
	0·866	1·294	67	4·13	9·86	42	4·5
	1·142	1·493	76	12·38	25·60	48	4·9

though the capacity existed for their being taken on by the system in some animals to a greater extent than in others. However this may be, a striking fact is brought clearly into view—namely, that the assimilative power of the system in general over these sugars can count as almost nothing compared with the assimilative power that must evidently be in operation in connection with the occurrence of absorption as

a normal procedure from the alimentary canal. Looking at the relative position that the three monosaccharides hold in relation to disappearance from view through the instrumentality of the system, galactose shows itself to be in a decided manner less susceptible of appropriation than the other two. According to the figures in the table lævulose was thrown off to about a midway extent between galactose and dextrose. The order followed by the three agrees with that observed after the one grm. per kilo. intravenous injection.

The position of maltose appears at first sight to be very remarkable. In the one grm. per kilo. intravenous injection experiments maltose was thrown out of the system with the urine to a rather larger extent than lactose. In the subcutaneous injection experiments it is seen to stand pretty nearly in the same position as dextrose. Reference has been made to maltose being carried by the agency of the glucase present in the mucous membrane of the intestine into glucose at the time of absorption. Glucase is stated to have been found to a certain extent in the blood. It may be concluded that it cannot exist there to any material extent, looking at the figures that were obtained after the intravenous injection of maltose. If any notable conversion of maltose into glucose had taken place in the blood, it may be rationally assumed that the urinary figures would not have stood in the position they did. Introduced into the subcutaneous tissue the sugar elimination for maltose and dextrose is approximately the same. I think the conclusion may be drawn that in the subcutaneous tissue the maltose must meet with an adequacy of glucase to effect its conversion into glucose before absorption. In a subcutaneous injection the solution passes virtually into a lymph-space structure and here falls in contact with active protoplasmic matter which may be said to mean presence of various kinds of enzymic power.

I have previously spoken of the influence exerted by the system in the direction of carrying glucose into a lower form of cupric oxide reducing carbohydrate. With the array of evidence presented there can be no doubt of the occurrence of this change. It is, indeed, one that stands in a line with

the transmutation of glucose into glycogen. The power of the living system to perform this latter operation no one for a moment disputes. In the case of the other event there is a much less extent of action involved, but, as I have said, the action that occurs is in the same direction. Evidence of its occurrence is afforded both by the subcutaneous injection experiments and after the intravenous injections where limited amounts of dextrose were employed. With the injection of large amounts of dextrose no effect is visible, presumably on account of the changed dextrose being concealed from view by the large presence of unchanged material. Galactose does not appear to be altered in the same way. Neither after the subcutaneous nor the intravenous injections is there any decided indication of a lower cupric oxide reducing body being produced. In the case of lævulose the disclosure of information is defeated by the destructive action exerted by the process of boiling with the acid. It follows, if a loss of lævulose occurs, that this would prevent the display of any increased cupric oxide reducing effect that might be produced.

As to the method by which the dextrose is moved into a lower cupric oxide reducing body something requires to be said. We have long been familiar with the movement of carbohydrate matter in the opposite direction through the agency of enzymic action, and until recently enzymes have been looked upon as only capable of hydrolysing or breaking down. Latterly, however, they have been viewed as possessing wider power, and are now regarded as taking part in the process of building up as well as in that of breaking down. Croft Hill in 1898 was the first to adduce evidence of the possession of synthetic as well as analytic power by enzymes. He showed that the same ferment might, according to the existing conditions, operate in the direction of breaking down or in that of building up. The play of reversible ferment action has been confirmed by the observation of others, and it seems to have now attained the position of an accepted doctrine. If by reversible enzyme action the molecules of a monosaccharide can be made to combine and become built up into molecules of higher construction, there is nothing

unintelligible in dextrose passing, when brought within the sphere of influence of protoplasmic matter—the source from which enzymes take their origin—into forms of carbohydrate of less cupric oxide reducing power.

The deduction to be drawn from what has preceded is that saccharose, lactose, and maltose, reaching the circulatory system as such, remain untouched and simply filter off with the urine. Their molecules, it may be considered, are not of a nature to possess attraction for, and to be taken on by, the bioplastic molecules with which in the circumstances they are brought into contact. Galactose, lævulose, and dextrose, on the other hand, must be regarded as possessing an affinity for bioplasm which renders them susceptible when similarly placed of being to a greater or less extent assimilated or taken on by it instead of being wholly rejected. Although thus much is permitted to be said, yet the experimental evidence which has been adduced shows that the conditions existing only lead to a more or less tardy and incomplete assimilation, whence it arises that even in the case of dextrose, the most assimilable of the three sugars, a certain amount of escape occurs with the urine.

The experiments with the injection of a quarter of a grm. of dextrose per kilo. are instructive upon this point. The blood from the instantly killed animal gave the figures 2·400 per 1000 before and 2·660 per 1000 after hydrolysis; that from the animal killed five minutes after, 2·333 and 2·910 per 1000; and from the animal killed at the end of fifteen minutes, 1·430 and 2·040 per 1000. With the introduction of even so small an amount as $\frac{1}{4000}$th of the body weight, after the lapse of a quarter of an hour the blood had not returned to its normal condition, but the sugar present in it had a lower cupric oxide reducing power than it had in the first experiments. In the case of the animals that were allowed to live for sixty minutes after the injection the blood also showed in an unmistakable manner the existence of a larger amount of sugar than is normally present. From this it follows that when sugar reaches the circulation, instead of being at once appropriated, it only makes a tardy disappearance and during this time its presence is being revealed by the state of the urine. Looking

at the table showing the condition of the urine secreted during the sixty minutes, the amount of sugar is seen to stand definitely higher than in normal circumstances. In one instance the figures stood at 12·56 per 1000 before and 18·20 per 1000 after hydrolysis. There was an instance in which the figures stood at 2·28 and 5·67 per 1000, which is in conformity with the normal, but here there was quite an exceptional flow of urine, and reckoning for outflow and proportionate amount present, the quantity of sugar found constituted 11·3 per cent. of that injected. Some of this would be naturally due to normal sugar elimination.

Instructive results were likewise given by the one grm. per kilo. subcutaneous injections. Here the sugar would only be gradually absorbed, and even at the end of two hours, when the animals were killed, examination of the subcutaneous tissue at the seat of injection showed that marked sugar impregnation still existed. The blood at the time named gave a distinctly higher indication of sugar than is normally found. The urine varied considerably, which is not surprising, as there are many factors that influence the secreting activity of the kidney. Where large quantities of sugar are eliminated the diuresis evoked forces elimination, but in contrary circumstances, through inactivity of the kidney, only a restricted outflow may occur. To quote the highest sets of figures obtained before and after hydrolysis, they ran as follows: 11·20 and 22·40 per 1000, 16·30 and 22·80, 13·60 and 24·00, and 12·38 and 25·60.

I consider that the evidence supplied by the line of research to which I have just been referring unequivocally shows that sugar reaching the circulation cannot escape filtering off with the urine on passing through the kidney, and yet it is contended that the carbohydrate of our food finds its way through the circulatory system in the form of sugar to the tissues for consumption. If this really occurred it could not fail to be attended with glycosuria. Undoubtedly, however, the carbohydrate must in some way or other reach the tissues, for it is here where utilisation of it occurs.

The information supplied by the respiratory quotient

affords evidence of the carbohydrate of the food actually reaching the seat of utilisation in the tissues. With carbohydrate matter consisting of carbon, and of hydrogen and oxygen in the proportion to form water, there is only the carbon free for oxidation, and the oxygen utilised gives rise to an equal volume of carbon dioxide. Thus, if carbohydrate were the only material oxidised the intake of oxygen and the output of carbon dioxide would stand equivalent. In the case of fat and proteid there are other elements to undergo oxidation, and thus a portion of the intake of oxygen will be applied to this purpose and render the output of carbon dioxide proportionately less. Now, observation shows that the larger the amount of carbohydrate entering into the constitution of the food, the nearer, in accordance with the principle expounded, does the respiratory quotient approximate to the unity point.

From these considerations the difficulty has to be faced that the carbohydrate of the food has to reach the tissues and that if it passed, as has hitherto been taught, through the circulatory system in the form of sugar, it would flow off with the urine as it does in diabetes. Let us suppose for a moment that the food carbohydrate really took the course that has been mentioned. Could this possibly occur without any indication of it being afforded by the state of the blood and the urine? We have seen that no definite relationship is to be traced in the healthy animal between the food and the state of the blood and the urine. It is true that the amount of blood sugar came out rather higher for the rabbit than for the cat, the mean of the observations recorded being 1·089 per 1000 before hydrolysis and 1·495 per 1000 after for the one against 0·880 and 1·140 per 1000 for the other; but in the case of both animals the figures stood decidedly higher for the thoroughly fasting than for the fed state, being 1·21 per 1000 before hydrolysis and 1·64 per 1000 after for the rabbit, and 1·10 and 1·15 per 1000 for the cat. As regards the urine, the same order occurred in the fed state as was noticeable for the blood, the figures being 3·69 per 1000 before and 7·03 per 1000 after hydrolysis for the rabbit, and 2·75 and 5·87 per

1000 for the cat. In the fasting state the urinary figures were 2·23 per 1000 before and 4·80 per 1000 after hydrolysis for the rabbit, and 4·19 and 8·65 per 1000 for the cat.

Without any food, then, to supply sugar for transit through the circulation, the amount of sugar in the blood is seen to be higher than when food was being taken. There is much variation in our own food at different times, but the urine reveals nothing to show it. Voit gives as a normal daily diet for man 118 grms. of proteid, 56 grms. of fat, and 500 grms. of carbohydrate. The urine with this diet gives no further evidence of the presence of sugar than after animal food or no food at all. Can the 500 grms. of carbohydrate pass through the circulatory system to the tissues in the form of free sugar without affording evidence of its doing so through the medium of the urine? We have seen from the experiments with the intravenous injection of a quarter grm. of dextrose per kilo. how sensitive the urine is to the presence of sugar in the blood, and surely the transit of 500 grms. *per diem* in the human subject from the food ought not to leave the urine in the same state as when there is no food carbohydrate passing, as would happen in a day of fasting. I am not oblivious of the alleged glycogenic function of the liver, but if the liver detained the carbohydrate and subsequently gave it out as sugar this would not prevent the system from being, at some time or other, traversed by the sugar, with the result of a proportionate appearance of sugar in the urine.

It is necessary for service in the economy that the food carbohydrate should reach the tissues, but the transport must be in some other way than as free sugar in the blood, seeing that sugar passing to the tissues would at the same time pass to the kidney and filter off with the urine as it does in diabetes. If sugar entered the blood, nothing short of immediate assimilation by it would suffice to prevent the kidney being reached, but assimilation is spoken of as taking place in the tissues, and this involves passage of sugar to them through the circulation.

I do not think the distinction between assimilation and

utilisation is kept as clear as it should be. Often it seems as if, from the manner in which the word "assimilation" is used, it implies utilisation. In reality it only implies a taking into, and incorporation with, the material that performs the assimilative duty. Utilisation is a subsequent process and it need not necessarily take place immediately. The one is a process of synthesis which has come to be regarded as dominated by enzyme action, for to enzyme action is now assigned the office of governing factor of building up as well as of breaking down; the other is a process of breaking down with which oxidation is associated. Both the material to be oxidised and the oxidising agent enter the molecular complex within which the oxidation occurs, not presumably in a direct manner by one step but by successive steps of degradation with the formation of various intermediate products before carbon dioxide, water, and ammonia are reached.

It may be said, therefore, that both oxygen and the material to be oxidised are assimilated by the bioplastic molecule within which they constitute the basis for metabolic action. Evidence is afforded of oxygen being taken and stored up by the molecule, in a form to be ready for use when required, by the increase of weight that has been observed to occur in a marmot during profound hibernation, and by the discharge of carbon dioxide that has been noticed to persist for some time from a frog placed in an atmosphere of nitrogen and therefore cut off from obtaining an intake of oxygen. Without the storage to some extent of both foodstuff and oxygen by assimilation or incorporation into the molecule there would be no provision for stability of metabolic action.

Seeing that the requirement exists for the carbohydrate of the food to reach the tissues where utilisation occurs, and that it is incompatible with the circumstances that present themselves for it to pass through the circulatory system as free sugar, we are faced with the problem of how the transport is in reality made. This is the matter to which I will now proceed to direct attention, and I think it will be found that an explanation can be given which satisfactorily meets all the circumstances.

It has long been known, in connection with the vegetable kingdom, that a class of bodies exists into which carbohydrate enters as a component part. These bodies are called glucosides, and with the advance of chemical knowledge that has occurred they have been found to constitute a very numerous and widely distributed group. By chemical means the carbohydrate can be recovered from them, but in the characters they possess there is nothing for a moment suggestive of its presence, so completely does the carbohydrate lose its identity. Until recently it has not been surmised that a similar state of things holds good in connection with products from the animal kingdom. Landwehr at the commencement of the 1880-90 decade obtained a carbohydrate from mucin which he styled "animal gum." He invested his product with a variety of visionary attributes, but did not concern himself about it as a constituent of the parent substance. In the early part of the following decade, whilst engaged in the pursuit of my investigations upon the relations of sugar in the animal system, I came across evidence pointing to proteid matter, in connection both with the animal and vegetable kingdoms, being of a glucoside nature. The subject was dealt with in my *Physiology of the Carbohydrates*, published in 1894, having previously formed the subject of a communication entitled "On the Glucoside Constitution of Proteid Matter," presented to the Royal Society in the preceding year.

By the research conducted it was shown that carbohydrate was susceptible of being obtained from proteid by the breaking down action of both potash and sulphuric acid, the product in the former case presenting itself in the amylose form and in the latter as sugar. A demonstration was afforded, through the medium of the several distinguishing properties observed, that the product obtained was in reality of a carbohydrate nature. The albumin and vitellin of the egg, the proteids of the blood-serum, and fibrin, from the animal kingdom, and, from the vegetable kingdom, glutin from wheat flour, and the proteid of the haricot bean, all were found to yield cleavage carbohydrate. None was obtainable from gelatin and only an insignificant amount

from casein. To begin with, as is not unusual in like circumstances, dissent was raised to the proposition I had put forward, but I think it may be taken to be now generally accepted. Indeed, gluco-proteid is a term that has found its way into general use.

It was not the mere chemical fact of carbohydrate being a component of proteid that constituted the point of interest to me. I saw in it a bearing of deep physiological importance in connection with the application of carbohydrate within the animal economy, and it was this that riveted my attention to the matter. I knew that carbohydrate underwent utilisation in the tissues, and that a means of transport for it from the alimentary canal must exist that would not permit of its filtering off with the urine. The entry of carbohydrate into the construction of the proteid molecule I could see provided what was wanted, and gave the clue to the solution of the difficult problem that had hitherto faced us. Locked up in proteid, carbohydrate is in a safe position for freedom from being discharged with the urine, on account of the proteid molecule being too large to pass off by filtration.

The importance of the subject has prompted me to return to it and to conduct further work in connection with it. This I have been lately carrying out in the physiological laboratory of the University of London, where I have found every facility provided to aid its prosecution. The work has branched out into collateral channels and has called for a considerable amount of steady labour, in which I have received the able and zealous help of my assistant, Mr. Bywaters.

The first point to be dealt with is the presence of carbohydrate as a component part of different animal proteids. I will afterwards give attention to the physiological bearings belonging to the information that has been experimentally obtained. It will be understood that we shall be now looking at carbohydrate matter from an opposite point of view to that from which it has hitherto been commonly regarded—namely, as proceeding in the building up or anabolic instead of the breaking down or katabolic direction.

It is the locked-up carbohydrate that has to be searched

for, and the combination has to be broken down before any information can be obtained. After the carbohydrate has been set free, the next step is to place it in a position to be susceptible, not merely of recognition, but of quantitative determination. It is brought to the state of sugar for the attainment of the object in view, and in order that the sugar may be satisfactorily estimated there must be nothing finally present to interfere with the application of the ammoniated cupric test. I have now had much experience in connection with this matter and consider that with careful manipulation trustworthy results are obtainable. For years past I have been in the habit in blood examinations of estimating the amylose (proteid) carbohydrate as well as the sugar, and in my *Physiology of the Carbohydrates* I made special allusion to the fact of an increase being observable as an accompaniment of the presence of an augmented amount of sugar, looking as though a portion of the sugar had passed into an assimilated state whilst in the blood.

The proteid carbohydrate may be separated by the breaking down agency of potash and by that of hydrochloric acid. With the ordinary proteids the results given by the two processes on subsequent estimation fairly agree. In the case of the mucoids, however, there is great disparity, and the information supplied throws light, as will be subsequently seen, on the constitution of the molecule.

Something requires to be said regarding the method of procedure for estimating the amount of proteid carbohydrate present in different circumstances, as the matter is related to a line of investigation which seems to me to have a promising character, and which, as yet, has not been touched by others, and is therefore not to be found referred to in books.

Estimation of Proteid Carbohydrate by the Potash Process.

When liquid blood is the material to be analysed about 30 grms. is a convenient quantity to employ. After being weighed out into a 400 c.c. flask, it is treated with a potash

solution so as to give to the mixture a 10 per cent. strength. In the case of the solid proteids, from $1\frac{1}{2}$ to 2 grms., and in that of dried blood, 3 grms., may be taken. After thorough drying, the material requires to be brought to a minutely divided state in order to secure full action of the chemical agent, which is an essential point. The reduction is effected by rubbing down in a mortar and passing through a fine metallic gauze sieve (90 to the linear inch). The weighed product is next treated with about 35 c.c. of a 10 per cent. potash solution and subjected to boiling for half an hour under a reflux condenser in a flask of about 400 c.c. capacity, which provides against the inconvenience arising from the foaming that occurs. The contents of the flask are now poured into ten volumes of methylated spirit (95 per cent.) contained in a tall beaker, and the flask is rinsed out with more spirit. The beaker is allowed to stand till the following day for the precipitate to settle. Filtration is next performed through asbestos arranged in a Gooch's perforated porcelain crucible adapted to an exhausting filter pump. Much time is saved by decanting the clear liquid and filtering this first, as the precipitate, directly it is poured on to the filter, clogs it and impedes filtration. After washing with spirit, the next step is to subject the precipitate, which contains the proteid carbohydrate in the amylose form, to the hydrolysing influence of a boiling mineral acid. Hydrochloric acid of 5 per cent. strength is used for this purpose. The precipitate is washed with the hot acid, which dissolves it, from the asbestos plug in the crucible into the beaker originally used for precipitation, the last traces being removed by repeatedly pressing out the liquid from the asbestos by squeezing it with a glass rod against the side of the crucible. After heating the acid solution in the beaker to the boiling point to get rid of the adhering traces of spirit, the liquid is transferred to a small flask (about 150 c.c.), into which the washings of the beaker are also poured. The contents of the flask, measuring about 50 c.c., are next boiled for one and a half hours under a reflux condenser. When cold, the liquid is nearly neutralised with potash, clarified by

boiling with hydrated alumina,[1] made to 75 c.c., and thrown on to a dry filter. The filtrate is rendered faintly alkaline by the addition of a drop or two of strong alkali, filtered from any slight precipitate, and titrated with the ammoniated cupric test. The liquid for titration should be of a pale sherry colour, and should give no biuret reaction on being titrated. Summarily stated, the process consists of breaking down the proteid with potash, precipitating the liberated amylose carbohydrate by means of spirit, converting into sugar, and estimating this in the usual way.

Estimation of Proteid Carbohydrate by the Hydrochloric Acid Process.

In the potash process when blood is taken, it is not essential that it should be first of all treated with spirit to remove the sugar, as the potash exerts a destructive action upon it, and in this way gets rid of it. Such is not the case with the acid process, and before treatment with the acid the removal of the sugar present must be effected. The blood (say 30 grms.) should be extracted and washed with methylated spirit with the use of a press as in the process adopted for the quantitative determination of sugar in blood. The coagulated mass obtained is treated with the required amount of strong hydrochloric acid and allowed to stand overnight to become thoroughly liquefied, then diluted down to a 10 per cent. strength, having reckoned for 100 c.c. volume as the quantity to work with, and afterwards boiled under a reflux condenser for one and a half hours. A dark-coloured liquid is obtained containing the nitrogenous products of disintegration as well as the sugar. The point now to be attained is to remove the nitrogenous products and to leave the sugar. Here a certain amount of difficulty is encountered on account of the soluble nature of the principles to be dealt with. Phosphotungstic acid is the best precipitant. A 20 per cent. solution is added till it no longer gives a precipitate. The resulting admixture

[1] *Vide* Pavy, "The Quantitative Estimation of Sugar in Blood," *Journal of Physiology*, vol. xx, 1896.

is heated to boiling for the purpose of facilitating subsequent filtration by causing the precipitate to assume a more granular form. What is next wanted is to remove the phosphotungstate compound; but as this is not completely insoluble, and particularly when hot, the process is more lengthy than it would otherwise be, and at the same time steps must be taken to provide as far as possible against loss of sugar by its remaining attached to the precipitate. Hence filtration (best on what is known as a glass filter plate), rubbing down in a mortar, and adequate washing are required to be performed. Subsequently the liquid obtained, after being nearly neutralised with sodium hydrate, is evaporated down over a water bath to a small bulk and allowed to stand overnight for settlement out to occur. Filtration is now conducted with asbestos, a Gooch crucible, and an exhausting pump, the washing being effected with a saturated solution of sodium chloride to prevent any phosphotungstate precipitate being taken up. The filtrate has now to be made slightly alkaline with sodium hydrate, and as this is done a deep blue colour is developed. The colour that is developed might perhaps, without the employment of litmus or other such-like agent, suffice to indicate that alkalinity has been reached, but in my own work it has not been deemed prudent to rely upon it for this purpose. On exposure to air the colour disappears and the disappearance is accelerated by passing air through the liquid. All that remains to be effected now is to bring to a known volume, as, for instance, 75 c.c., throw on to a dry filter, and titrate. When properly prepared, the liquid is colourless and gives no biuret reaction on titration.

Having described the processes for quantitatively determining the proteid carbohydrate obtainable by the breaking down action of potash and hydrochloric acid, I will now proceed to deal with various products, and to show how they stand under subjection to the treatment in question.

PROTEID CARBOHYDRATE OBTAINED BY CLEAVAGE WITH POTASH AND HYDROCHLORIC ACID. (THE FIGURES IN EACH CASE REPRESENT PARTS PER 1000, WITH THE CARBOHYDRATE EXPRESSED AS GLUCOSE.)

Dried Defibrinated Blood (Serum and Corpuscles) from the Horse.

The blood was defibrinated, poured into methylated spirit, the coagulum collected, pressed, washed with boiling spirit, dried, and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
21·9	19·7
20·4	20·8
21·2	20·7

Dried Plasma of Horse's Blood.

The blood on collection was treated with 1 per cent. strength of citrate of potash to prevent coagulation, and centrifugalised. The plasma was afterwards dealt with in the manner described for the defibrinated blood.

Cleavage by potash.	Cleavage by hydrochloric acid
25·8	26·6

Dried Blood Corpuscles.

The corpuscles were obtained by centrifugalising the citrated blood and washing with normal saline solution. They were then treated with spirit and subsequently prepared in the usual way. The first two sets of figures refer to horse's blood, and the last two to cat's blood.

Cleavage by potash.	Cleavage by hydrochloric acid.
4·5	3·2
3·3	2·9
4·5	1·9
5·2	2·5

It is noticeable that the yield of proteid carbohydrate by

the corpuscles is in striking contrast with that yielded by the other portions of the blood, the amount being quite of an insignificant character. It may be remarked with regard to the lower figures obtained after cleavage by hydrochloric acid in comparison with those after cleavage by potash that the bulky phosphotungstate precipitate, from the difficulty offered in thoroughly washing out the sugar, may have had something to answer for in connection with the result.

Looking at the relative yield from the defibrinated blood and plasma, it is in accordance with what might be looked for in view of the presence of the corpuscles in the former and not in the latter case.

Serum Globulin.

The colourless serum from horse's blood was treated with an equal volume of saturated ammonium sulphate solution. The precipitate was collected, treated with water to dissolve, and the globulin reprecipitated with ammonium sulphate. Water was again added to dissolve, and the globulin was now precipitated from the liquid by boiling. The coagulated globulin was afterwards washed with boiling water to remove the saline matter and then treated with boiling spirit. It was finally dried and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
28·1	28·1
30·5	30·2

Serum Albumin.

The filtrate from the serum globulin just dealt with was diluted with water, and, after acidifying with acetic acid, heated to boiling. The coagulated albumin was collected, pressed, and adherent ammonium sulphate washed out with boiling water. After treatment with boiling spirit, it was dried and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
18·4	17·7
20·8	19·3

Globulin, it is thus seen, gives a higher yield of proteid carbohydrate than albumin, but this is all that can be said. Contrary, therefore, to a statement opposed to my original results which I find is obtaining currency in print, albumin gives a notable yield.

Blood Fibrin.

The clot from horse's blood was washed with water till practically colourless. It was then dehydrated with boiling spirit, and afterwards dried and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
25·8	23·1

Egg Proteids.

The egg proteids, alike from the yolk and the white, do not materially differ as regards their yield of carbohydrate except in one instance—viz., ovomucoid, in which a very different state of things exists from that met with ordinarily. Not only in this instance is the yield of carbohydrate signally large, but apparently it is derived from a double source—viz. from carbohydrate in the form of sugar, and likewise from carbohydrate in the amylose form. The matter will be subsequently discussed under the head of Ovomucoid, but I refer to it now as it probably affords the explanation of the difference in the results obtained from the crude material of the egg and the isolated proteid principles.

Crude Egg Yolk.

The egg yolk was treated with methylated spirit and the precipitate repeatedly boiled with fresh quantities of spirit with the view of getting rid of the major portion of the fat. The yolks were not completely freed from adhering white, which may possibly account for the higher figures after the acid cleavage.

Cleavage by potash.	Cleavage by hydrochloric acid.
27·0	32·7
25·3	29·9
26·7	31·9
27·9	30·7

Egg Vitellin.

Egg yolk was treated with an equal volume of saturated ammonium sulphate solution so as to bring to a state of half saturation. After being allowed to stand for some hours to settle out, the precipitate was collected and boiled up with spirit, and the process again gone through. The precipitate was then washed with boiling water and subsequently dealt with in the usual way.

Cleavage by potash.	Cleavage by hydrochloric acid.
32·1	30·7

A second specimen was prepared by extracting the egg yolk with ether to remove the fat, dissolving the residue in 10 per cent. sodium chloride solution, filtering, and precipitating the vitellin by diluting with water. The precipitate was collected, washed by decantation with water, then with boiling spirit, afterwards with boiling water, and finally again with spirit, after which it was dried and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
29·0	25·6
30·0	27·7

Crude Egg White.

Dry commercial egg albumin was dissolved in a small quantity of water and the proteids precipitated by the addition of methylated spirit. The precipitate was washed with boiling spirit and afterwards dried and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
29·1	42·3
28·4	45·8

A second portion of the dry commercial egg albumin was dissolved in water, slightly acidified, and then boiled. The precipitate was collected, washed with boiling water, and afterwards dehydrated with spirit, dried, and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
27·9	44·6, 42·6 Duplicates.
28·0	44·6, 43·6 Duplicates.

A third product was obtained from the whites of fresh eggs treated in the same way as the last.

Cleavage by potash.		Cleavage by hydrochloric acid.
27·2	. . . .	$\left\{\begin{matrix}44·0\\48·7\end{matrix}\right\}$ Duplicates

It will be noted in all these instances that the yield from the acid cleavage is considerably higher than that from the potash. The presumable explanation is contamination with ovomucoid, which, as will be subsequently seen, yields much higher figures with the acid than with the potash cleavage. In the first set of instances given, ovomucoid would be evidently carried down, as it is precipitable, like albumin, with spirit.

Crystallised Ovalbumin.

The whites of fresh eggs were beaten up and mixed with an equal bulk of saturated neutral ammonium sulphate solution. After standing about twelve hours, the slight precipitate (globulin) produced was separated by filtration, and saturated ammonium sulphate solution was added to the filtrate until a slight permanent precipitate was produced. This was dissolved by the addition of a few drops of water and then one-fifth normal sulphuric acid was pipetted in drop by drop until the solution was just opaque. After twenty-four hours, the crystalline precipitate was filtered off and recrystallised by solution in water and treatment with ammonium sulphate and sulphuric acid. The recrystallised product was dissolved in a large quantity of water, acidified with acetic acid, and coagulated by boiling. The coagulated albumin was collected, washed with boiling water, then with boiling spirit, and afterwards dried and powdered. Two preparations were made and analysed.

	Cleavage by potash.		Cleavage by hydrochloric acid.
(i)	26·2	. . . .	25·0
(ii)	$\left\{\begin{matrix}23·5\\22·5\end{matrix}\right\}$ Duplicates	. . .	$\left\{\begin{matrix}25·7\\24·8\end{matrix}\right\}$ Duplicates.

Conalbumin.

This name has been applied[1] to a form of albumin found in the mother liquid after the separation of the crystallised ovalbumin. It is present in conjunction with ovomucoid. From the filtrate obtained after the removal of the crystallised ovalbumin, the conalbumin and ovomucoid were salted out by the addition of solid ammonium sulphate. On redissolving in water, acidifying, and boiling, the conalbumin was coagulated, whilst the ovomucoid remained in solution. The conalbumin was collected, washed with boiling water, and subsequently with boiling spirit.

Cleavage by potash.		Cleavage by hydrochloric acid.	
26·1 22·1	Duplicates	34·1 36·9	Duplicates.

Ovomucoid.

The liquid from which the conalbumin had been separated by filtration was evaporated to dryness, whereby the ovomucoid was rendered gelatinous and insoluble in cold water. After repeatedly washing with cold water and boiling with spirit, it was collected, dried, and powdered.

Cleavage by potash.	Cleavage by hydrochloric acid.
107·9	215·9

Ovomucoid obtained by another mode of preparation was also dealt with. Dry commercial egg albumin was dissolved in about fifteen times its weight of water, acidified, and boiled in order to coagulate the albumin, which was removed by filtration. From the clear filtrate evaporated on the water-bath to a small bulk, the ovomucoid was precipitated by the addition of two volumes of methylated spirit. After washing repeatedly with boiling spirit, it was collected, dried, and powdered.

	Cleavage by potash.	Cleavage by hydrochloric acid.
(i)	59·1	150·9
	61·1	149·2
(ii)	73·6	210·0
(iii)	43·9	133·0
	42·6	134·7
	33·4	119·0

[1] Osborne and Campbell, *Journal of the American Chemical Society*, vol. xxii, 1900.

Other specimens of ovomucoid were prepared from the whites of fresh eggs instead of commercial egg albumin. Five different samples were obtained and submitted to examination.

	Cleavage by potash.	Cleavage by hydrochloric acid.
(i)	79·8	186·0
	76·9	215·0
(ii)	110·0	220·3
	140·4	227·0
(iii)	125·0	265·0
	141·5	260·0
(iv)	123·3	217·0
(v)	144·9	255·8
	145·5	220·9
	188·3	231·0

Osseo- and Tendo-mucoid.

In order to ascertain if other mucoids correspond with ovomucoid in the relative results given after cleavage by potash and by acid, steps were taken to obtain specimens of osseomucoid and tendomucoid. The process is a tedious and lengthy one, but specific directions have been given by Hawk and Gies[1] for osseomucoid, and by Cutter and Gies[2] for tendomucoid, and these were strictly followed. At first it appeared as if there would be a want of success in obtaining the products, but by perseverance in adjusting the acid to the requisite point to produce their precipitation from the half-saturated lime-water extracts that had been previously made, and by allowing time for the gelatinous form of precipitate produced to settle out, the difficulty was overcome. The subjoined were the results obtained on subjecting them to the potash and the acid processes of treatment.

Osseomucoid.

Cleavage by potash.	Cleavage by hydrochloric acid.
46·1	107·6

Tendomucoid.

Cleavage by potash.	Cleavage by hydrochloric acid.
32·9	116·2

[1] *American Journal of Physiology*, vol. v, 1901.

[2] *Ibid.*, vol. vi, 1901–2.

The same order of figures, it is seen, is observable as for the ovomucoid, but the proportionate amounts were less. It may be that this arose from the presence of incidental impurity.

Have we not something in these results which speaks suggestively upon the point of the molecular constitution existing? With ordinary proteids the figures, except in the instances where ovomucoid is liable to be present as an impurity, are practically about the same after the potash and the acid cleavage. This may be expected to be the case if the carbohydrate is present in the proteid molecule in the amylose form. In this form it is simply liberated without being destroyed by the boiling potash, and, after being hydrolysed by the acid treatment, it is estimated as sugar. With the acid cleavage the amylose carbohydrate would, at the time of cleavage, be hydrolysed into sugar and thus present itself at once in the form of sugar. In the case of the mucoids the figures after the potash cleavage are seen to be conspicuously less than those obtained after cleavage by the acid. The proteid molecule is regarded as consisting of a central intrinsic part with side-chain attachments, and sugar side chains, I think, have been hinted at if they have not been shown to exist. The facts before us seem to me to be suggestive of sugar side chains being present in the case of mucoids. Should they be so, they would be acted upon and destroyed by the potash and not by the acid on being cleaved off, and thus the smaller potash yield becomes intelligible. After boiling with 2 instead of 10 per cent. potash, a much larger yield of carbohydrate is obtained. This appears to arise from some of the mucoid escaping being broken down. Whatever does so would fall like amylose carbohydrate when poured into spirit, and on subsequent boiling with the acid, cleavage would occur with attendant appearance of sugar.

I have been speaking of the proof afforded, by the agency of chemical breaking down action, of the presence of carbohydrate as a constituent of proteid matter. I will now speak of the information supplied in connection with this point

through quite a different channel—through a channel which bears on action occurring within the living system. Phloridzin, a crystalline principle obtainable from the bark of the stem and root of the cherry and some other allied trees, is known to produce a strongly glycosuric effect when introduced into the system either by the alimentary canal or by intravenous or subcutaneous injection. The glycosuria produced by it differs from the glycosuria arising from other causes in not being due to antecedent hyperglycæmia. In ordinary glycosuric conditions the sugar of the urine is derived from sugar existing in the blood and filtering off with the urine. They are thus associated with hyperglycæmia, and this bears a proportionate relation to the sugar elimination. In phloridzin glycosuria, however, no such relationship exists. Indeed, it was said at one time that there was less sugar than normal to be found in the blood. This, as a matter of fact, is not true, and the statement depended upon the defective mode of analysis adopted. Some years ago I gave careful attention to the matter, and published my results in a communication, "On Phloridzin Diabetes," contained in the *Journal of Physiology*.[1] It was there shown that the sugar almost invariably stood somewhat above the normal, a condition probably attributable to the passage of some of the sugar formed in the kidney into the blood flowing through it.

After intravenous and subcutaneous injections of phloridzin the glycosuria follows very speedily and may be very intense. In one of my experiments the urine contained 112 per 1000 of sugar two hours and twenty-five minutes after a subcutaneous injection. The blood in this case only contained a trifling excess of sugar—a state that could not possibly account for the elimination that occurred. The effect only lasts whilst there is phloridzin present to exert an action, but it may be renewed by a fresh administration. The result occurs in the absence of food. Even after prolonged fasting glycosuria has been found to have been produced.

Everything points in this form of glycosuria to the kidney

being the seat of the production of the sugar, and through the work that has been undertaken, a relation has been noticed to exist between the nitrogen and sugar discharged. In the fed animal, with a store of glycogen in the liver and other parts of the body, the sugar is in high and irregular proportion to the nitrogen, but by starvation it becomes reduced, and is ultimately brought to a constant ratio. At first there is a discharge of the loosely combined carbohydrate existing in the system, and whilst this is going on the sugar elimination bears an uncertain relation to that of the nitrogen, but subsequently, when the carbohydrate referred to has been swept away, the two become drawn from proteid disintegration, and now the period of fixed relationship is reached. Assuming that this point has been arrived at, and that the source of both the sugar and the nitrogen is the disintegrating proteid molecule, the relationship between the two ought to afford a basis for calculating the proportionate yield of sugar derivable from the disintegrating molecule. The nitrogen eliminated corresponds with a given amount of proteid disintegrated. In the dog, when the condition is brought to proteid as the only source of the sugar and nitrogen eliminated, the relation has been stated to stand at 3·8 of the former to 1 of the latter, and upon this relationship the amount of sugar yielded works out at about 60 per cent. of the proteid disintegrated. The ratio of 2·8 to 1 has been more recently asserted[1] to constitute the correct D : N value. Calculating upon this basis, the percentage of carbohydrate yield stands at about 44 instead of 60.

Such is the proposition that has been advanced, and it gives a vastly greater carbohydrate component part in the proteid molecule than is given by chemical destructive action. It is evident, however, that the conditions under which cleavage occurs are essentially different in the two cases, seeing that in the one the carbohydrate simply comes straight off, whilst in the other the opportunity exists for the occurrence of intra-molecular action. When carbohydrate enters

[1] Stiles and Lusk, *American Journal of Physiology*, vol. x, 1903.

a molecule rearrangements ensue, and it may temporarily assume another grouping. There is abundant evidence to show that carbohydrate may enter a molecule and, through regroupings within, may come out in the form of fat, and conversely fat may enter and carbohydrate be split off.

Up to the present I have been looking at the evidence in support of carbohydrate entering into the constitution of proteid from the side of cleavage action. There is another aspect, however, from which the matter may be regarded, and this is from the side of construction.

A single instance may be taken to suffice for showing that carbohydrate is susceptible of being built into proteid. Yeast cells may be regarded as little masses of bioplasm, and we only know of bioplasm in connection with proteid as a basis. Placed in a nutrient medium, the bioplasm grows and forms fresh bioplasm by incorporating into itself the molecules with which it is adapted to unite. Pasteur showed that yeast cells would grow, which means would form proteid, in a medium consisting of sugar, ammonium tartrate, the ash of yeast, and water. It may reasonably be here inferred that the sugar contributes to the formation of the proteid, but no absolute proof of it is afforded, seeing that the elements of the sugar—carbon, hydrogen, and oxygen—are also present in the ammonium tartrate. Ammonium nitrate, it has been found, may be substituted for the ammonium tartrate, and when this is done the only source for the carbon entering into the constitution of the proteid is from the carbon existing in the sugar. Thus proof is furnished of sugar being turned to account in connection with the construction of proteid.

With the knowledge supplied by the fundamental details that have been considered, I will now proceed to discuss the conclusions that it appears to me may be drawn therefrom. Absorbed from the alimentary canal and utilised in the tissues, how does carbohydrate pass from one locality to the other without giving evidence of its transit through the circulation by the filtering action occurring in the kidney? This is the problem that we have now to consider, and I think it will be found that we need not go further than the seat of absorption

to meet with its solution. Let us closely examine the operations that can be shown to be here taking place.

We have seen that the object of digestion in preparing food for absorption is to break down the large molecular constituents of it and thus carry them from the colloidal into the diffusible state. It was formerly considered that this is all that is requisite, absorption being regarded as taking place in compliance with the laws of osmosis. The effect of modern research, however, is to show that it is by the instrumentality of cell action instead of by physical osmosis that the products of digestion pass into the system. Waymouth Reid, by means of a number of well-devised and carefully conducted experiments, has demonstrated that the integrity of the intestinal epithelium is necessary for the proper procedure of absorption. In the concluding paragraph of a paper on "Intestinal Absorption of Solutions"[1] he says, with reference to glucose, "It appears, from a study of the absorption of weak solutions of glucose, that, with the intestinal membrane as normal as the experimental procedure will permit, phenomena present themselves which are as distinctly opposed to a simple physical explanation as are those previously studied in the absorption of serum." Selective action has even been shown to be exerted in the absorption of salines, and sodium chloride has been found to be taken up in a manner that can only be accounted for by special cell appropriation.

Absorption by cell action may be said to mean bioplasmic incorporation. The absorbed material passes into and becomes a component of the living matter. In other words, it is assimilated or made to form a part of bioplasm in process of growth. Now, for bioplasmic growth it is requisite for the molecules which are taken on to be of appropriate configuration to become attached to the large and complex biogenic molecules of which they are to form a part. In the absence of the proper configuration they remain untouched, or, otherwise expressed, fail to be assimilated. Thus, in the process of digestion, not only is it necessary, as I have previously stated, that large molecules should be broken down into small

[1] *Journal of Physiology*, vol. xxviii, 1902.

ones to give the property of diffusibility for the sake of penetration, but also that the molecules produced should be of such construction as to be adapted to unite with those into which they are intended to become incorporated. It is the province of the enzymes supplied by Nature to bring about this adaptation, and unless it is brought about there can be no combination. Saccharose molecules, for instance, have not the requisite conformation for being taken on by the biogenic molecules of protoplasm, and unless there were enzyme action to put them into the state of monosaccharide, they would remain untouched, and simply be absorbed and pass through the system unchanged.

What I have said about preparation by enzyme action for being taken on by bioplasm applies to each of the food principles—proteid, carbohydrate, and fat. They all undergo breaking down into a molecular form suited to enter into combination with the bioplasm with which, at the seat of absorption, they are brought into contact. This having been accomplished, the process that follows is one that may be designated bioplasmic growth, and to this I will now direct attention.

Examination of the small intestine, the chief seat of absorption of the products of digestion, reveals a mucous membrane provided with an immense number of small projecting processes known as the villi. Each villus is provided with an epithelial covering, and in the central part there is found lymphoid tissue, containing lymphocytes, and capillary blood-vessels. The lymphoid tissue, a meshwork of intercommunicating spaces, gives origin to a vessel or vessels constituting an initiatory component of the lacteal system. The superficial epithelial cells, and the lymphocytes met with in the lymphoid tissue, are the structures which, I think I shall be able to show, play an all-important part in connection with the absorption of nutrient matter.

The epithelial cells belong to the columnar type. In the fasting state they are seen to be characteristically of this form and to present a granular appearance with a well-defined central nucleus. In the actively absorbing state

they sometimes undergo alteration. Many of them may be observed to have lost their columnar form and to have assumed more or less of a spheroidal shape. They at the same time become charged with fat which is visible in very various-sized globules and granules. In this state the cell may present a close resemblance to the secreting cell of the liver which also is concerned with fat production. I entered into this subject in my *Physiology of the Carbohydrates*, 1894, under the head of "Transformation of Carbohydrate Matter into Fat," p. 245 *et seq.*, and gave photo-engravings to illustrate from the rabbit the fatty condition assumed by the villus cell after the ingestion of starchy food consisting of oats. Many of the cells were literally gorged with fat. At the present moment I will not follow this question further. Let it suffice to say that in connection with the bearings of fat it is specially the epithelial cells of the villus that are concerned.

We now come to a component of the villus which I look upon as playing a most important rôle in connection with the train of phenomena associated with the passage of food to service in the economy. I refer to the lymphocytes which are present in the lymphoid tissue belonging to the parenchyma of the villi, and likewise in the submucous lymphoid tissue throughout the intestinal tract. They constitute small actively growing and proliferating cells which greatly increase in number during the period of absorption of food. Kölliker,[1] as far back as the middle of the last century, writing about them said: "While digestion is going on, we frequently find the whole parenchyma of the villi densely filled with nuclei, here and there surrounded by cell membranes [lymphocytes are evidently meant], elements which are, perhaps, never entirely absent in a villus, but are at other times far fewer." It is only in connection with the small intestine that this special condition is found. Both in the case of the stomach and large intestine a marked difference exists, no more lymphocytes being visible than may be seen in lymphoid tissue elsewhere.

Recently the lymphocyte question in relation to food has

[1] *Manual of Human Histology*, Sydenham Society Translation, vol. ii, p. 98.

been looked at from another point of view. Many workers have been giving close attention to the corpuscular elements of the blood, and a branch of study has been established which has already yielded much valuable knowledge, and gives promise in the future of yielding more. When lymphocytes reach the blood, as may be considered their natural course to do, they fall into the generic group that has long borne the name of leucocytes. In former times but little was known about this group of bodies, but latterly, by staining and improved manipulative procedure for microscopic examination, means of differentiation have been afforded and different kinds of leucocytes are now enumerated. The lymphocyte is easily distinguishable from the other leucocytes, and thus it can be made the subject of study in relation to varied bodily conditions. Now, by the counting observations that have been conducted, it has been found that the blood undergoes considerable alteration with respect to the number of lymphocytes present as a result of the effect of food.

From the concurrent testimony of many observers it may be looked upon as a settled point that the lymphocytes become greatly increased in number in the blood after the ingestion of food. They show a continuous rise up to about the fourth or fifth hour, and then a more or less rapid fall. Gulland[1] speaks of the total number of lymphocytes per cubic millimetre having been found to have been increased by from 3,000 to 11,000. This must mean a large accession of proteid matter to the blood as a result of food absorption. From 3,500 to 4,000 per cubic millimetre is mentioned as having constituted the ordinary starting-point before food. Variable rates of increase are given by others, but the general admission is that a very notable increase occurs. The condition, in fact, is of a sufficiently established nature to have received the designation of digestion lymphocytosis.

This flow of lymphocytes into the blood naturally means, as I have already said, a great accession to it of proteid matter. Pohl[2] has given the calculation, which I may mention with-

[1] *Brit. Med. Journ.*, vol. ii, 1904, p. 584.

[2] *Archiv für Experimentelle Pathologie und Pharmakologie*, Band xxv, 1889.

out expressing any opinion as to the value, one way or the other, to be attached to it, that 15 grms. represents the amount of proteid that may thus reach the blood after a meal.

Lymphocytes consist of proteid, and proteid contains locked-up carbohydrate. In this way lymphocytes become mixed up with carbohydrate metabolism. There is no doubt about the lymphocytes reaching the blood as a sequence to the absorption of food. Examination of the blood obtained by a needle-prick through the skin suffices to demonstrate the connection. Prevailing ideas, however, regarding the mode of transit stand in a very tangled state. Looking at the perfection of the arrangement which Nature has provided for the purpose it is strange that this should be so. Until some thirty years ago the lacteal system was regarded as constituting the channel for the transport of the absorbed nutrient matter from the alimentary canal into the blood, just as the general absorbent system was looked upon as conveying the unutilised portion of the pabulum that had escaped from the blood-vessels into the lymph-spaces for the nourishment of the tissues. The confusion, I think, dates from Schmidt-Mülheim's work[1] in which the thoracic duct was ligatured and the urinary nitrogen elimination after nitrogenous food estimated and compared with that found in instances where the duct was free. According to the results given no essential difference was discernible. It would be out of place here to discuss this matter, but I have looked into it and do not see that it by any means satisfactorily establishes the deduction that has been drawn and that has driven physiologists, in seeking for something else, to take refuge in what I feel may be spoken of as the impossible.

As a substitute for the view allocating the passage of the lymphocytes to the lacteal tract, it has been suggested—and the idea carries credence at the present time—that they reach the circulation by traversing the walls of the capillary vessels. Even in the most recent work, we find observers looking in the mesenteric veins for the lymphocytes produced in the villi. Could there be any conception more opposed to physical

[1] *Archiv für Anatomie und Physiologie*, 1877.

laws? Picture a lymphocyte, constituted as it is, passing from a lymphoid lacuna through the walls of a capillary against the pressure existing within. It is intelligible for leucocytes to pass through, as is known they do, in the opposite direction under the influence of the capillary blood-pressure existing, just as mercury may be forced through the pores of chamois leather, but to traverse a membrane with pressure in operation against them seems to me to be nothing short of an impossibility. Presumably, it may be further said, even with proteid molecules, that the same governing factors bring about a corresponding result. Because under the capillary pressure, and apparently in proportion to it, proteid passes from the vessels into the lymph which bathes the tissue elements, it does not follow that it should be possible for the reverse to occur, or, in other words, for the proteid that has escaped nutritive appropriation in the lymph-spaces, wherein there exists a lower pressure than in the capillaries, to pass back in a direct manner into the blood.

It is not disputed that lymph corpuscles are to be found in the contents of the lacteal vessels, but it is considered that they have not been found in sufficient quantity to account satisfactorily for the digestion lymphocytes that reach the blood. There is a point in connection with looking for them that appears to me not to have received proper attention, at all events I have never seen it alluded to. In the process of coagulation the lymphocytes become entangled in the coagulum in the same manner as occurs with the corpuscles of the blood, and the place to look for them is hence in the coagulum and not in the fluid. I am in the habit of preventing coagulation by the employment of a little citrate of potash, and thus the examination is rendered much easier.

The fact of lymphocytes being discoverable within the lacteal system affords proof that transport through this channel occurs. I can state from my own observation that they are to be found throughout the different parts of the lacteal system. It is not difficult to obtain chyle for microscopic examination that is on its way to the mesenteric glands, and I can distinctly assert that lymphocytes are recognisable

in it. They appear to be more numerous after the glands have been traversed. If lymphocytes are to be found passing along Nature's channel, it shows that this track is in actual use for the purpose, and hence it follows that any other mode of transit would be simply supplementary instead of one of absolute necessity. Now, seeing that the imaginary supplementary transit stands totally in antagonism with physical laws, can it for a moment be allowed to retain the position it at present holds? The granules constituting the molecular base of chyle and likewise fat globules pass. Of this there can be no possible doubt. Why, then, should there be any question existing with regard to the lymphocytes? The channel is more than sufficiently capacious to meet what is wanted for their passage, and if some passed, why should not all do so?

The flow through the lacteals is greatly increased at the digestion period. Although the contrary may have been asserted, yet in reality the matter does not admit of dispute. At a period of full fasting the vessels are not to be seen and are probably in a more or less completely empty state with attendant stasis. During active digestion and absorption, on the other hand, they stand out conspicuously, and when incised give immediate exit to an abundant flow of chyle. In harmony with this state the villi are more prominent and loaded with lymph-corpuscles. Notwithstanding former denials, it may be considered that present-day work is in accord with this assertion.

The villi, then, may be regarded as a propagating and rearing ground for the lymph-corpuscles I have been considering. They grow, I would say, upon the nutrient matter derived from the digested food, like yeast-cells grow in a suitable pabulum, or bacilli in a culture medium. Developing in this way and travelling along the lacteal tract, they become carriers of assimilated food principles into the system, and reaching the circulation, pass under the denomination of digestion lymphocytes. I will not at the present moment enter into the question of what subsequently becomes of these corpuscles. As yet I have only dealt with them

morphologically, but I have to speak of the chemical bearings belonging to them, and it will be convenient to reserve what I have to say about their destination until after these have been considered.

Lymphocytes consist virtually of little masses of bioplasm, and the property of bioplasm is to assimilate or to incorporate within itself matter which is suited for the purpose. They may be compared to unicellular organisms, and may be said to grow independently upon the nutrient matter around them. In this growth the molecules of the nutrient matter become linked on to the proteid molecules of the augmenting bioplasm in a manner to lead to the extension that ensues. For this, a reciprocal relation must exist between that which is taking on and that which is taken on, and it is by enzyme action that provision is made for bringing about the required relationship condition. This having been effected, the union takes place by virtue of affinity—a power by which atoms and molecules are drawn into chemical combination, and therefore a power of supreme importance in the domain of chemistry.

We know how some atoms and molecules when brought together enter into chemical union whilst others show no disposition to do so. We know also where affinity exists that it does so under very varying degrees of strength. The effect of affinity is conspicuously realisable in the inorganic kingdom. It is not so self-evident in connection with the organic kingdom, but, nevertheless, I take it that it stands at the foundation of the combinations that occur. The expansive power of a growing structure may be very great, as is made manifest by the damage of building constructions sometimes perceived to be occasioned by the growth of trunks and roots of trees. I remember upon one occasion having seen a heavy paving stone raised out of place by a ramified fungus growth underneath. Instances of this kind bring home to us the fact that in the molecular combination associated with growth there must be no mean amount of attraction force at work.

In the lymphocyte bioplasm, then, there exists the aptitude

for taking on the food molecules to which the requisite configuration has been given by enzyme action. Peptone is representative of the nitrogenous portion of the food and glucose of the carbohydrate. They both are found on absorption to disappear. Hofmeister,[1] commenting on the disappearance of peptone, suggested that it was taken hold of by the lymphocytes, and that, bound up in these, it could traverse the circulatory system without filtering off when passing through the kidneys. Pohl[2] speaks of the proteid of the food being first broken down by digestion and then built up again by the lymphocytes into the proteid specifically belonging to the animal in which the action occurs. The lymphocyte, he adds, must subsequently become dissolved in blood-plasma or be taken by the tissues. A. Mathews, in an article on the "Origin of Fibrinogen,"[3] enters into the question of the transformation of food proteids into blood proteids, refers to Schmidt's and Mörner's observations pointing to paraglobulin being derived from disintegrating leucocytes, and himself adduces evidence suggestive of leucocytes being the source of fibrinogen.

All this touches upon the point that is before us, which is the function of the lymphocyte in assimilating digested foodstuff, and what subsequently becomes of the assimilated material. It will be noted that in the views of the various authorities which have been mentioned reference is only made to the peptone product of digestion. I have to suggest that the action should be extended and made to embrace carbohydrate—that carbohydrate and peptone stand upon the same footing as regards the manner in which they are dealt with by the growing bioplasm of the intestinal lymphocytes—that both become linked on to the biogenic molecules of the lymphocytes and thus made to enter into the constitution of living matter in which the various chemical changes of metabolism are wrought out. Hofmeister's remark about peptone being placed by the assimilative action of the lympho-

[1] *Zeitschrift für Physiologische Chemie*, Band v, 1881.

[2] *Loc. cit.*

[3] *American Journal of Physiology*, vol. iii, 1899.

cytes into a position to traverse the circulation without filtering off with the urine applies with equal force to sugar, of which it may, without hesitation, be said that if it is to be available for service in the economy it must not be permitted to enter the circulation in the small molecular form represented by sugar.

Under the view set forth the food principles are, in the first instance, constructed by assimilative action into the principles of the blood. The step that follows is that the tissues derive their nourishment from the elaborated principles of the blood. The blood feeds upon the food supplied from without, and the tissues feed upon the blood. I do not see that we can deny to the blood, with the standard composition it possesses, an inherent assimilative power comparable to that possessed by the tissues. I take exception to the view expressed in a recent communication to the Pathological Society by Professor W. D. Halliburton.[1] Reference is made in it to the success that has attended Emil Fischer's efforts to synthesise some of the lower cleavage products of proteolysis, and it is suggested that a more complete breaking down of proteid occurs in the alimentary canal than has been hitherto supposed, erepsin being specified as the enzyme which has the power of carrying peptones into more rudimentary cleavage products. The new theory is stated to assume a complete breaking down of the foodstuffs previous to their being built up into living tissue. What, it may be asked, would be the condition of the blood if such a view held good? Instead of constituting as it does a component of the system, with as much of a standard composition as muscle and other allied structures, it would consist of an agglomeration of small molecules in transport to the tissues, and, in their transport, in a position to filter off with the urine in passing through the kidney. What, also, would be the use of the elaborated proteids of the blood if the broken-down foodstuffs were directly conveyed to the tissues and there synthesised? As far as I can see, everything stands against the correctness of such a view, and what may be said clearly to be wanted is

[1] The *Lancet*, March 18th, 1905, p. 717.

that the synthesis should take place preparatory to entry into the blood.

Because the chemist can, as yet, only synthesise the more rudimentary molecules into higher combinations, it is not to be argued that Nature is in the same position. We lack the power of forging the implements by which Nature's work is performed. When we get hold of and apply these implements—as, for instance, when we operate with enzymes—we can achieve in our laboratory experiments the same that is effected inside the living organism. There are grounds for believing that chemistry works upon the same basis in the organic and the inorganic kingdoms of nature. Affinity and adaptability in molecular configuration are at the root of chemical union, and the difficulty in bringing about a desired chemical union, in manipulating with the complex organic molecules, is intelligible when we look at the intricacy of the conditions that require to be met with respect to molecular configuration. Fischer's simile of lock-and-key arrangement in the fitting together of molecules brings home to us the severity of the conditions that must exist where highly complex molecules are dealt with. The slightest deviation in any particular from the required construction would suffice to throw the adaptability for union out. If the adaptability for union between the complex peptone molecule and the taking-on molecule of the lymphocyte bioplasm exists—and I consider there are good grounds for believing it does—there would be no reason for the proteolysis of digestion to be carried to a further stage.

Let me show how the line of argument that has been set forth harmonises with what is taught in connection with the chemistry of the doctrine of immunity. For this I will quote from Ehrlich's Croonian lecture, published in the 'Proceedings' of the Royal Society for 1900, and will premise by stating that foodstuff and toxin molecules are looked upon as standing in an allied position in relation to the assimilating protoplasmic molecules. At p. 433 Ehrlich says: "We may regard the cell quite apart from its familiar morphological aspects and contemplate its constitution from the purely

chemical standpoint. We are obliged to adopt the view that the protoplasm is equipped with certain atomic groups, whose function especially consists in fixing to themselves certain foodstuffs of importance to the cell life. Adopting the nomenclature of organic chemistry, these groups may be designated side chains. We may assume that the protoplasm consists of a special executive centre (Leistungs-centrum) in connection with which are nutritive side chains which possess a certain degree of independence and which may differ from one another according to the requirements of the different cells. And as these side chains have the office of attaching to themselves certain foodstuffs, we must also assume an atom-grouping in these foodstuffs themselves, every group uniting with a corresponding combining group of a side chain. The relationship of the corresponding groups, *i.e.* those of the foodstuff and those of the cell, must be specific. They must be adapted to one another as, *e.g.*, male and female screw (Pasteur) or as lock and key (E. Fischer). From this point of view we must contemplate the relation of the toxin to the cell."

I have spoken of the digestion lymphocytes as little collections of bioplasm growing upon the prepared nutrient principles of the food. I consider that in the exercise of their assimilative or taking on office they deal alike with the products derived from proteid and from carbohydrate matter, and therefore what is said about the action occurring in the one case is applicable to the other. Do not the other leucocytes belonging to the blood stand in a similar position in relation to assimilative action ? The phagocytes have acquired a renowned reputation through their power of devouring bacilli and other foreign particles, and subsequently disposing of them in the same way that the amœba engulfs its food and then digests and makes use of it. This means that assimilation is brought into play, and if assimilation is thus put into operation it is only reasonable to infer that it can be applied to surrounding molecules of any description that possess the requisite conformation for being assimilated. Upon such ground, the leucocytes may be regarded as constituting the

assimilative agency or the living element of the blood, giving to it the general power that is possessed by living matter elsewhere. Thus, products which may incidentally reach the blood, either from ingestion or from the tissues, that are susceptible of utilisation, may become assimilated and placed in a position to be subsequently made use of. The lymphocytes of the lymphoid tissue, I take it, may be regarded as performing the same kind of duty by assimilating whatever utilisable products of retrograde tissue metamorphosis they may chance to meet with, and thus rendering them fit for further use.

We now come to a point which, although an important one, seems to have received but scant consideration by physiologists. In what way do the fibrinogen, globulin, and albumin of the blood take origin? They are highly complex proteids and can only be conceived to arise through the instrumentality of bioplasm. Applying the mind to the matter, the following train of reasoning suggested itself to me. I took it for granted that they may be considered as having a close connection with the food, and that there must be some intermediate living agency in operation to produce them. Seeing that lymphocytes constitute a living growth constructed out of the elements of the food, that there is an active flow of them into the circulation connected with food ingestion, and that there is afterwards a melting away of them to be observed, it seemed that in these circumstances a groundwork was presented suggestively affording a solution of the problem before us. May we not look to the gland cell to help us analogically in the matter? The gland cell consists of bioplasm which, in this instance, has grown upon nutrient matter derived from the blood. As part of its life it undergoes autolysis and gives its formed material to its associated secretion. Lysins now constitute a well-known class of implement constructed by Nature for the execution of her work, and it may be taken that a special lysin is provided for each of the different operations to be carried out. By autolysis of the lymphocytes the material built up by them from the elements of the food would be given to the blood, and may not the autolysis occur in such a manner as to lead to the evolution of the proteids of the

blood, which in their pabulum character stand in an intermediate position between the food and the tissues? That tissue is in reality built up and maintained by proteids, such as those in the blood, is shown by the fact that in the egg they unmistakably constitute the medium from which the tissues of the developing chick derive their nutrient matter. Food into lymphocytes, lymphocytes into proteids, proteids into tissue substance, may be taken as representing the chain of physiological connection between the food and the tissues.

In support of the view that has been expressed I have found, on looking through the literature of the subject since the idea was framed, that A. Mathews,[1] to whose work I have already alluded, has adduced experimental evidence in favour of leucocytes constituting the source of fibrinogen. In his paper it is also to be noted that he refers to the work of Alexander Schmidt[2] pointing to the likelihood of the paraglobulin of the blood being derived from leucocytes, and likewise to that of Lilienfeld and Miescher[3] suggesting the same source for the serum albumin.

The point that has been discussed has a bearing on the application of proteid to energy production. It has long been known that the elimination of urea stands in relation to the proteid food ingested, and it is considered that the proteid molecule splits up into a non-utilisable nitrogenous portion which is discharged as urea, and a complementary utilisable residue which, whether assuming the form as has been suggested of carbohydrate or not, may be reckoned to contribute to energy production. It has been difficult to conceive that this combustion proteid passes into the tissues for the purpose of being broken down. Looking upon the process as occurring within the lymphocyte, there is nothing that appears incongruous, and it is noticeable that the increased urea elimination about harmonises with the period of maximum lymphocyte autolysis.

As yet I have only spoken of the assimilation of carbo-

[1] *American Journal of Physiology*, vol. iii, 1899.

[2] *Zur Blutlehre*, Leipsic, 1892.

[3] Hoppe-Seyler's *Medicinische-Chemischen Untersuchungen*, Band iv, p. 441.

hydrate by being built up into proteid through the agency of bioplasm. Probably, when there is no particularly large supply of carbohydrate to be dealt with, this is the main result that occurs. When, however, the supply is extensive it is evident that some escapes being disposed of at the seat of absorption, and thence reaches the portal blood. At a period of fasting, and likewise after the ingestion of animal food, the portal blood, as regards the amount of sugar present, corresponds with that belonging to the other parts of the circulatory system. After a free supply of starchy food, however, sugar may be found to be present in the portal blood to a considerably larger extent than anywhere else. In my *Physiology of the Carbohydrates* I entered somewhat fully into this matter, and gave a number of experimental results obtained under different conditions with regard to food. The presence of about 2 per 1000, or a little over, was of not uncommon occurrence. In two instances figures standing as high as 4 per 1000 were met with.

The sugar which escapes assimilation at the seat of absorption and reaches the portal blood is conveyed to the liver, wherein it is brought into close relation with the cells of the organ. By these it becomes absorbed and transmuted into glycogen. There is overwhelming evidence to show that this action occurs, and if it is complete, as it ought to be, sugar from the food is prevented reaching the general circulation. It will be seen from the arrangement existing that there is a double provision against the entry of sugar from the food into the general circulation. Whatever may pass the first line of obstruction has to confront the arresting action of the liver. In this way security is provided against the systemic blood receiving an influx of sugar at every meal into which carbohydrate enters.

I look upon glycogen as simply a cleaved off storage material standing in identically the same position as fat. I think it may be said that it is right to consider that the sugar is taken on by the bioplasm of the cells and by it transmuted into, and thrown off as, glycogen. This kind of operation is one of the commonest of the operations occurring in con-

nection with living matter. Starch, cellulose, and a multiplicity of other products are cleaved off from a pre-existing biogenic complex into which something other than the cleaved off principle has passed in. Ordinary enzyme action is attended with taking on in one form and throwing off in another. Looked at in this way, there is nothing mysterious or incomprehensible about the position that glycogen holds, and its position in the liver is not different from that which it holds in the numerous other localities in which it is met with. Its presence only means disjoined carbohydrate collected as redundant material in the locality where it is found. The supply of carbohydrate is in excess of utilisation and the surplus is thrown off as glycogen for temporary storage. Yeast-cells contain glycogen, and it has been noticed that when growing in a 1 per cent. solution of glucose there is only a small amount to be found present, whilst when growing in a 10 or 20 per cent. solution there is much. In the case of the liver it is common knowledge that its glycogen varies with the amount of carbohydrate food-supply. Diminishing the consumption going on, by reducing the activity of a part, promotes accumulation, and conversely, increasing the activity leads to diminution. For instance, division of the nerve or tendon of a muscle is followed by an accumulation of glycogen, and tetanising the muscle by a diminution.

By severe forced exercise it is found that glycogen may be made to disappear, alike from the liver and muscles, in the course of a few hours without any show of the production of sugar. The seat of actual consumption is in the muscles, and therefore in the case of its disappearance from the liver, there must be transport in some way or other through the circulatory system. To this point I will give attention.

The outcome of all modern work is pointing in a very strong manner to the taking on and throwing off capacity of organic matter, constituting an exceedingly widespread principle of action. I have purposely said "organic" and not "bioplasmic" matter, for in the action of enzymes, which can hardly be considered as representatives of bioplasm, have we not a taking on in one form and throwing off in another

action to deal with? It is, indeed, difficult to see how the action of an enzyme differs from that which is ordinarily looked upon as constituting a special attribute of living matter. I may even go a step farther and say it is difficult to see how the illustrations which at the present moment are being brought forward by chemists under the head of inorganic ferment action differ in nature from the occurrences associated with ordinary organic ferment action.

Applying the principle of action to which I have been alluding to the point under consideration, the suggestion presents itself that sugar is taken on as a side chain by a proteid constituent of the blood and transported to the tissues, where it is taken off for subjection to utilisation. The suggested operation is identical with what occurs in connection with the transport of oxygen. Oxygen is taken on by hæmoglobin, and, in a state of combination, transported to the tissues, where it is taken off and applied to utilisation. Glycogen is a storage material consisting of very large molecules and therefore not adapted for shifting its position. I should think that the first action that occurs is the breaking down of its molecule into molecules of glucose which become instantly taken on by the alluded-to molecules of the blood. There may be concerted action between the breaking down and taking on processes, and that there is such in operation is rendered probable by the fact that there is no show of sugar in connection with the occurrence. Enzyme action, it may be considered, of necessity constitutes a part of the process, and the enzyme concerned, and set into motion as needed, may, in the presence of altered conditions, be intelligibly conceived to be capable of producing the deviation from the natural living state with respect to sugar that so quickly takes place as a post-mortem occurrence in the liver.

The phenomena connected with phloridzin glycosuria afford confirmatory evidence in relation to the view that has just been expressed. Volume XXIX, 1903, of the *Journal of Physiology* contains a communication by Pavy, Brodie, and Siau on the "Mechanism of Phloridzin Glycosuria," in which the point in question is dealt with. The conclusion we

arrived at from the experimental work performed was that the sugar eliminated is derived from the katabolic action of the renal cells on a constituent of the blood containing sugar in a locked-up state. This idea was previously mentioned at a meeting of the Pathological Society in April, 1902. Loewi [1] has expressed a similar idea and has even gone the length of suggesting that the sugar, which is ordinarily looked upon as being in a free form in the blood, is in reality in a loosely combined state when the blood is circulating in the body. We did not commit ourselves to agreeing with this proposition, although otherwise we stood in accord with him. It is clearly established that the glycosuria produced by phloridzin is not due to hyperglycæmia, and it hence follows that there must be something in the blood to yield the sugar. The first effect of the phloridzin is to sweep away the glycogen that is present in the different parts of the body. If this passed through the circulatory system as free sugar, there ought to be hyperglycæmia in proportion to the glycosuria, which there certainly is not. This being the case, the only conclusion that can be drawn is that the katabolised glycogen (sugar) enters into side chain or loose combination with a constituent (proteid) of the blood, and is thus conveyed to the kidney, where it is set free and eliminated.

For a great number of years cases of diabetes have from time to time been noticed to have been associated with disease of the pancreas, and the feeling has been entertained that a connection exists between the two. Experimental physiology has since stepped in and shown indubitably that diabetes is producible by extirpation of the pancreas, and the view has been formulated that normally the organ supplies an internal secretion which contributes to the proper disposal of carbohydrate matter in the system. To the islands of Langerhans have been assigned this function, and weighty evidence has been adduced in support of the correctness of the view that has been taken.

Lépine a long while ago contended that a glycolytic ferment was derived from the pancreas which was instru-

[1] *Archiv für Experimentelle Pathologie*, vol. xlviii, 1902, p. 410.

mental in effecting the destruction of the sugar assumed under the glycogenic doctrine to be constantly reaching the blood, and that the absence of the ferment was the source of diabetes. His view has not received acceptance, and I do not consider that I need further allude to it. More recently Otto Cohnheim has conjectured that the pancreas supplies an activator to the ferment which, he says, exists in the muscles for the oxidation of sugar. In view of the anticipated therapeutic value of his pancreatic product in connection with diabetes, it has been made a patented article. Much adverse criticism of his work, however, has been advanced, and I myself feel that the matter stands upon a wrong basis. With the assistance of Mr. Bywaters I have entered experimentally into the subject, and the evidence that has been obtained has not stood in support of his proposition.

The work that has been conducted by others has been directed to the side of the destruction of sugar. No one has viewed the subject from the side of assimilation of sugar, but it seems to me that this is the aspect from which it should be looked at. Enzyme action is concerned in building up as well as in breaking down, and an activator is wanted for enabling the bioplasm of the intestinal tract to perform its work in connection with the assimilation of the absorbed sugar. Let me proceed to explain the matter from the standpoint that I think it ought to be viewed.

It has been recently ascertained that enzymes are dual bodies. One portion is insoluble in alcohol, non-diffusible, and destructible at a boiling temperature. This probably is of a proteid nature. The other—the co-ferment or activator—is usually soluble in alcohol, diffusible, and can be boiled without losing its activity. It corresponds with the active agents that are obtained from the thyroid, suprarenal capsule, etc. A great advance was made when Buchner discovered that the expressed juice of yeast contained the ferment, zymase, which converts sugar into alcohol and carbonic acid. Harden and Young,[1] in experimenting with zymase at the Lister Institute, have found that a given quantity of fresh

[1] *Journal of Physiology*, vol. xxxii, 1904.

yeast juice has its ferment power doubled by the addition of an equal volume of boiled juice. This means that an extra quantity of the activator, which is powerless by itself, gives increased power to the ferment principle in the juice. In a further experiment the yeast juice was subjected to filtration through a Martin's gelatin filter. Neither the filtrate, nor the residue on the filter dissolved in water, was capable of inducing fermentation, but when they were mixed together they produced fermentation almost equal in extent to that produced by the original juice.

Let it be supposed that the activator supplied by the pancreas is wanted to enable bioplasm to take on, or to assimilate, sugar. It may be assumed that there is always a certain amount of it in normal circumstances distributed through the system and ready for use. I have long known that the introduction of sugar into the circulatory system was followed by the presence of an increased amount of amylose carbohydrate in the blood, and I commented upon the point in my *Physiology of the Carbohydrates*. With the information that is now before us, the idea is suggested that a portion of the introduced sugar is appropriated by the bioplasm of the leucocytes and converted into proteid carbohydrate. In connection with the matter I will draw attention to the subjoined tabular arrangement of results showing the amount of amylose carbohydrate found in the blood of rabbits taken ordinarily and in that of rabbits subjected to the experimental injection of sugars of the monosaccharide class—

Amylose Carbohydrate from Rabbit's Blood expressed as Glucose in parts per 1000.

Normal blood examples.	Time between injection and killing.	After intravenous injection of—			
		Saline solution.	1 grm. per kilo. of—		
			Dextrose.	Lævulose.	Galactose.
1·39	15 minutes	1·35	1·60	2·67	1·74
1·34	—	1·35	1·53	—	1·93
1·39	—	—	1·52	—	—
1·52	—	—	1·80	—	—
1·39	—	—	—	—	—
1·40	30 minutes	—	1·62	2·60	—
1·46	—	—	—	—	—
1·25	60 minutes	—	1·34	1·81	—
1·55	—	—	1·43	—	—
1·44	—	—	—	—	—
1·41	—	—	—	—	—

It will be seen that in no case did the amylose carbohydrate exceed 1·55 per 1000 in the normal blood, whilst in some of the instances after the injection of the sugars, the figures stand considerably higher. Dilution of the blood would be occasioned by the injection, and the effect of this, with the animal killed shortly afterwards, would be to reduce the proportionate amount of amylose carbohydrate. The condition found to exist at the end of sixty minutes is interesting. It shows that with the advance of time there is a tendency for the effect of the injection to work off.

In another set of experiments pancreatic extract was injected in association with the sugar. The extract was prepared by treating the pancreas, which had been previously pounded with sand, with water, boiling, and filtering. The amount of extract used was such as to give a relation of about one grm. of pancreas per kilo. of body-weight. The results have been arranged in a tabular form.

Amylose Carbohydrate from Rabbit's Blood expressed as Glucose in Parts per 1000.

	After intravenous injection of—			
Time between injection and killing.	Pancreatic extract alone.	Pancreatic extract and 1 grm. per kilo. of—		
		Dextrose.	Lævulose.	Honey sugar.
5 minutes	—	—	1·75	—
15 „	1·77	2·47	—	2·16
—	—	1·85	—	1·95
—	—	1·70	—	—
—	—	1·65	—	—
—	—	2·39	—	—
—	—	2·19	—	—
—	—	1·77	—	—
—	—	2·00	—	—
—	—	2·35	—	—
—	—	1·57	—	—
—	—	2·08	—	—
30 minutes	1·52	2·12	2·22	—
—	—	2·21	1·74	—
45 minutes	—	—	2·56	—

After raw extract of pancreas and 1 grm. per kilo. of dextrose, which immediately caused death, the figures given were 1·04 per 1000.

Other experiments were conducted in which the sugar and extract were injected subcutaneously instead of intravenously. The results have also been arranged in a tabular form.

Amylose Carbohydrate from Rabbit's Blood expressed as Glucose in Parts per 1000.

Time between injection and killing.	After subcutaneous injection of pancreatic extract and 1 grm. per kilo. of—		
	Dextrose.	Lævulose.	Honey sugar.
1 hour	1·63	2·30	—
—	2·09	—	—
—	1·52	—	—
2 hours	1·77	—	1·49
—	1·83	—	1·74

Taken altogether, a long list of experimental results is here presented for grounding a judgment upon. The same method of procedure was adopted in all the experiments. Unmistakably different figures are seen to have been obtained after the injection of pancreatic extract and sugar from those yielded in the other experiments. The effect of the employment of the pancreatic extract is suggestive of its holding a corresponding position to the activator in the yeast juice experiments that have been referred to. It will be noticed that in one of the experiments raw pancreatic extract was employed and that immediate death followed. In this experiment there was no elevation of the figures.

I have only dealt with one of the methods of disposal of carbohydrate in the animal system. There is another, and it evidently must be regarded as holding a highly important position. I refer to the transformation of carbohydrate into fat, a process upon which an extensive industry is founded, seeing that it is at the basis of the fattening of animals with carbohydrate food. I gave consideration to this process in my *Physiology of the Carbohydrates* and showed that the superficial epithelial cells of the villi, and the liver-cells, may be regarded as constituting the operative agents. To the lymphoid cells, then, of the villi I assign the office of meta-

bolising carbohydrate into proteid, and to the epithelial cells that of metabolising it into fat.

A few words in conclusion regarding diabetes. Viewed from the standpoint that I have taken, it is the result of a wrong carbohydrate metabolism on the side of assimilation, and, in some cases, on that of breaking down as well. In the "alimentary" form of the disease the carbohydrate fails to be properly assimilated and prevented reaching the circulatory system in the small molecular state of sugar. In the "composite" form there is defective assimilation, and at the same time a faulty tissue breaking down. The carbohydrate, which has been locked up in combination, instead of passing on to proper oxidation, becomes liberated as free sugar, and thence escapes from the system as waste material. As long as carbohydrate is properly assimilated, and sugar is thus prevented reaching the general circulation, there can be no sugar passing into the urine from the food. Let the assimilative process fail, and immediately sugar finds its way into the circulation and thence into the urine, just as if it had been directly introduced by an intravenous injection.

APPENDIX.

THE ASSIMILATION OF CARBOHYDRATE INTO PROTEID AND FAT.

The following appendix consists of supplementary remarks on the lymphocytes of the intestinal villi viewed as assimilative agents of peptone and carbohydrate, and on fat production from carbohydrate within the epithelial cells of the villi. In both cases the remarks are accompanied with the confirmatory evidence afforded by photo-micrographic illustrations.

The outcome contended for in the preceding pages is that carbohydrate is assimilated at the seat of absorption and thereby placed in a position to be prevented reaching the general circulation as free sugar, instead of being conveyed to the circulation as sugar, as has been hitherto taught in accordance with the tenets of the glycogenic doctrine.

Observation shows that the passage of sugar into the systemic blood is attended with a proportionate passage into the urine. With its small molecular constitution, sugar cannot be kept, in the same manner as proteid is, within the bounds of the circulatory system, on account of its filtering off in company with water whenever an escape of the latter occurs.

Thus, sugar in the blood means sugar as a concomitant result in the urine, and if sugar reached the system, as it is stated to do under the teachings of the glycogenic doctrine, the glycosuric state belonging to diabetes would constitute

the universal condition—in other words, the pathological state would constitute the kind of condition existing if what is taken as representing the physiological course of procedure were actually carried out.

To prevent sugar from reaching the urine it must be prevented from reaching the general circulation. Hence the necessity for the assimilation of the food carbohydrate being effected before the general circulation is reached. The effect of injecting sugar in ever so small a quantity into the circulation is to produce a proportionate passage of sugar into the urine. In the case of the monosaccharides it is not to be considered that actually all the injected sugar passes into the urine. Evidence shows that a considerable portion is retained in the system, but the power of the system in general of assimilating or disposing of sugar is only of a gradually acting nature. Thus more or less time is required for the effect of the injection to pass off, and during this time the sugar present is exerting its influence upon the urine. There is always, no matter what the circumstances existing, a standard small amount of sugar present in the blood, and with this there is a corresponding small amount of sugar in the urine. Should an increase, from any cause whatever, of the amount of sugar in the blood occur, the condition of the urine will follow and serve as an indicator of what has transpired. In this way altered states of the blood with respect to sugar become revealed by the state of the urine.

Neither the blood nor the urine gives evidence of any perceptible sugar alteration as a result of the ingestion of carbohydrate food. With the occurrence of carbohydrate assimilation before the general circulation is reached the opportunity is not afforded for free sugar to become transmitted from the food to the systemic blood, and if it is not transmitted to the blood it cannot be transmitted to the urine. The circumstances thus fit in rationally with each other, and as long as a full assimilation of food carbohydrate takes place in compliance with the procedure portrayed, the urine remains uninfluenced by the carbohydrate matter ingested. Should the process of assimilation, however, that ought

properly to occur, escape doing so, sugar will reach the general circulation in proportion to the amount of carbohydrate that has failed to be assimilated, and thence pass off with the urine.

The large amount of carbohydrate that can be ingested under healthy conditions without leading to a manifestation anywhere of the presence of sugar brings home to us the greatness of the assimilative power that must exist as an attribute belonging to the natural channel for the entry of food material.

If we pause and look at the phenomena occurring concomitantly with absorption, a point that most forcibly strikes the attention is the disappearance from view of the products of proteolytic and amylolytic digestion. Peptone is not to be traced into the blood; and as regards sugar, whilst it is true that it is to be traced into the portal blood when carbohydrate enters to any significant extent into the food, yet otherwise there is no essential variation in the condition of the portal blood from that of the blood belonging to other parts of the system. The sugar that does appear in the portal blood under the circumstances named constitutes sugar that has escaped being disposed of at the seat of absorption. It is conveyed to the liver and here its further progress is arrested by the transmutation into glycogen that occurs. There is reason to believe that the supplementary action of the liver in the disposal of sugar is not to any material extent called into requisition except where the amount of carbohydrate ingested is large, the power of assimilation at the seat of absorption mainly meeting under ordinary circumstances the demand.

I have alluded to the combined disappearance of peptone and sugar as a result of assimilation, and to the potency of the assimilative power in connection with alimentation carried out in a natural way being sufficient to check the passage of both principles into the general circulation. Not only, however, do peptone and sugar stand on like ground in this respect, but they also behave alike on being injected into the circulatory system. They both fail to disappear as they do

when absorption occurs from the alimentary canal, a fact which shows that the assimilative power met with in the blood is not comparable to that in operation in connection with natural alimentation. Ultimately they disappear, probably in great part through the assimilative agency of the white corpuscles, but in each case more or less time is required for the purpose.

Assimilation of Carbohydrate into Proteid by the Agency of the Lymphocytes of the Villi.

Occurring contemporaneously with the act of absorption there is an active growth of lymphocytes taking place in the interior of the villus, and it is suggested that these lymphocytes grow upon the digested products of the food—peptone and sugar—just as unicellular organisms (as, for instance, yeast-cells, etc.) grow upon the materials present in a suitable nutrient medium. In the act of growth proteid is formed which finds its way into the blood, and, it is submitted, gives rise by autolysis of the lymphocytes to the proteid constituents of this fluid.

Much confusion has in recent times existed in connection with the life-history of the lymphocytes, and also, it may be said, viewing the matter from a more general standpoint, with the manner in which proteid formed from the food reaches the blood. In olden times it was considered without any dissent that the nutrient matter derived from the food, both fatty and albuminoid, reached the blood through the lacteal system. Latterly, however, upon what I consider to be insufficient and untrustworthy grounds, the matter has been thrown into a highly chaotic state.

A large amount of literature exists upon the subject, and nothing could be more confused and contradictory than the evidence that has been adduced by different authorities; but, upon it, physiologists have been driven to consider that whilst the lacteal system gives passage to fat from the seat of absorption of the digested food, it does not give passage to proteid.

Fat is permitted to pass; but proteid, although the channel is as free and open to it as it is to fat, has to find its way from the lymph-spaces of the villus through the walls of the blood-vessels, with the opposing influence of the pressure of blood within in operation against the transmission. Further, even, it is taught that compact bodies like lymphocytes, in spite of the blood-pressure opposing them, penetrate the walls of the vessels to reach the blood within, and search is made in the mesenteric veins for the discovery of the bodies in question.

There is plain, simple, and direct evidence at hand, to which I will proceed to refer, which I take to be sufficient to override the evidence derivable from considerations of a collateral nature upon which reliance has been placed in arriving at the conclusions that have been framed. In reality, we need not go further than to the absorbent system itself to obtain proof that proteid is transmitted through the lacteals from the villi to the blood.

Microscopic examination is the agency by which the proof is afforded; and in order that the matter may be placed in a convincing position I will exemplify the verbal statements that are made with the self-speaking testimony afforded by photo-micrographic illustrations.

An ordinary examination of broken-up villi brings into view a large number of lymphocytes. The substance of the villus, indeed, is in great part composed of these cells. In the moist state they may be stained with hæmatein, methylene blue, or neutral red, and thus treated they become very conspicuous microscopic objects. Roughly, they may be spoken of as consisting of two kinds, large and small. The latter are infinitely more numerous than the former. They are described as constituting proliferating bodies, and, in view of the circumstances connected with them, they must have a very active power of growth.

An idea of the number of these lymphocytes present in a villus is obtained by looking at stained sections of the intestinal mucous membrane. Such representations of the villi of the small intestine of the rabbit, after the use of hæmatoxylin

and eosin stains, are supplied on Plates I and II. The impression that cannot fail to be given is that the assemblage of lymphocytes for the whole intestine must be regarded as amounting to an incalculable number.

The presence of the lymphocytes in the villi does not go further than show the amplitude of the source of production that exists. The lacteal system of vessels has to be appealed to for information regarding transit to the blood.

To obtain the desired information observation must be conducted upon the recently killed, or on the anæsthetised living, animal. The rabbit is the animal upon which I have for the most part experimented, and the usual procedure has been to kill by pithing and then lay open the abdomen and bring the small intestine and the mesentery into view. The absorbent vessels are looked for that run to, and pass from, the mesenteric glands, and on these being in turn snipped through with a pair of scissors their contents flow out and may be collected by being sucked up into a glass tube drawn out at one end to capillary dimensions. In this way, with the fed animal, ample for microscopic examination may be readily collected. To secure a satisfactory product for examination there is an essential point to attend to. Coagulation very quickly indeed takes place. It even does so, unless precautionary measures are taken to prevent it, whilst the process of collection is being carried out. Now, in the process of coagulation the lymphocytes become removed from the fluid part, just as in the coagulation of blood the corpuscles become removed from the serum. No one would look in the serum for the blood-corpuscles, and it is similarly fruitless to look in the liquid obtained from the absorbent vessels for the lymphocytes unless steps have been taken to prevent coagulation. There may be a few stray ones to be discovered, but the coagulum is the situation in which they are to be found.

The circumstance that has been alluded to may explain the prevalent notion that exists upon the subject of lymphocyte transport. I have seen nothing stated about the adoption of precautionary measures in connection with the method of

DESCRIPTION OF PLATE I.

Two photomicrographs of longitudinal sections of intestinal villi of rabbit at a period of full digestion, showing the lymphocytes contained in them.

The intestine was removed immediately after killing the animal by pithing, cut open, portions pinned out, cleansed with saline solution, and immersed in a formalin solution of 10 per cent. strength.

Sections were cut in the ordinary way and stained with hæmatoxylin and eosin. Magnified 120 diameters.

The lymphocytes in both figures are seen scattered through the villus and flowing as a stream through its centre, where a distinct, free channel for them appears to exist.

PLATE I.

FIG. 1.

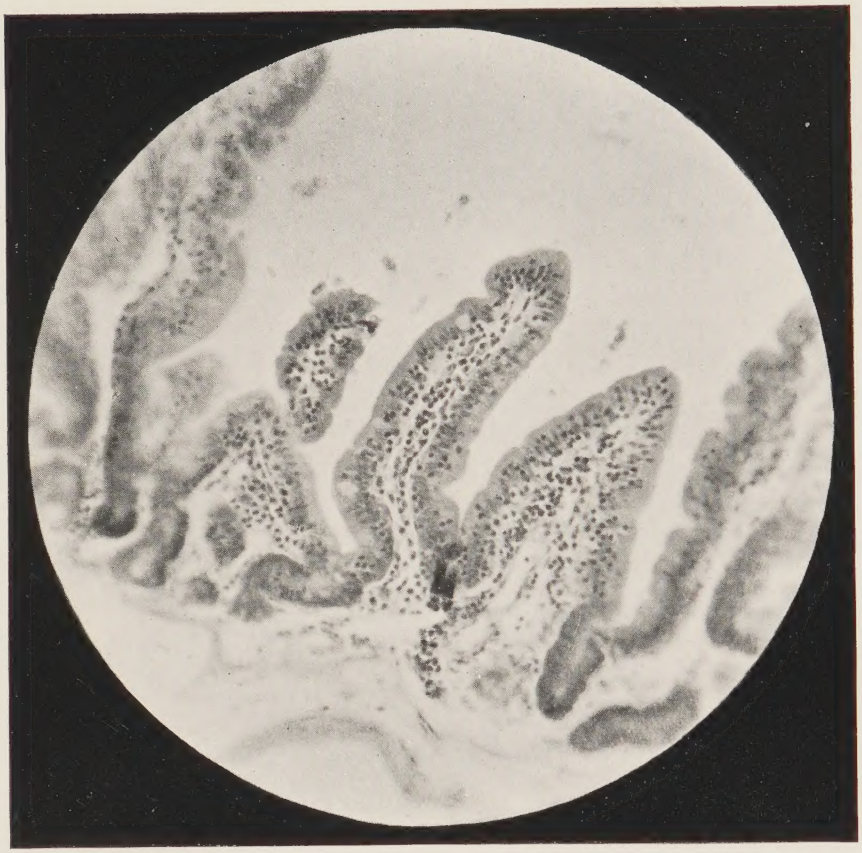
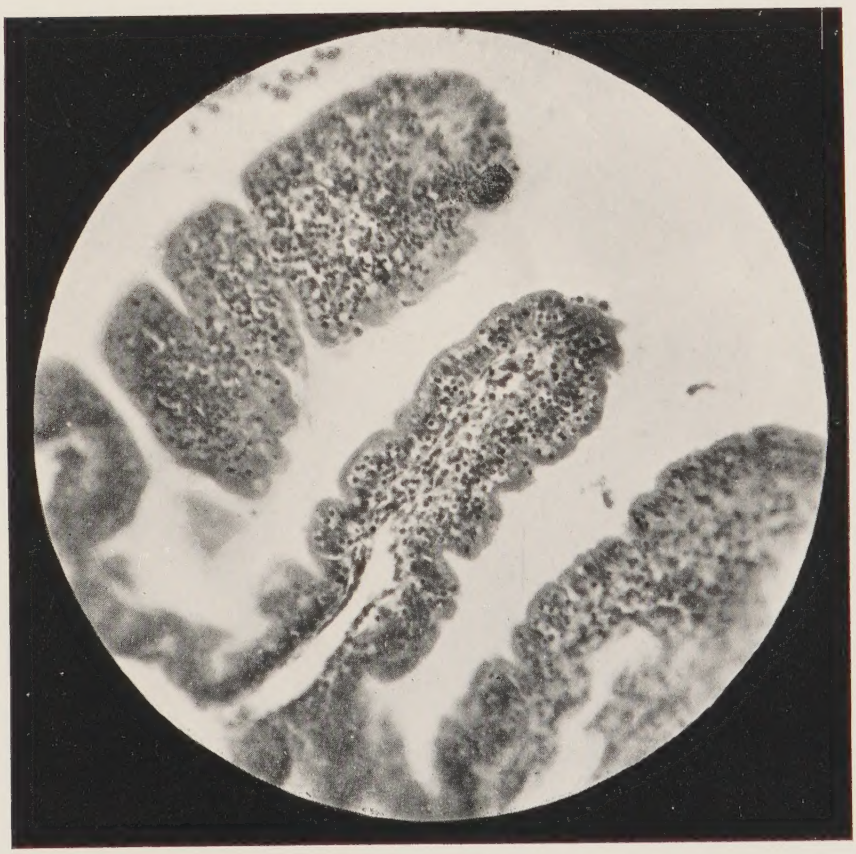


FIG. 2.



Lymphocytes in intestinal villi.

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DESCRIPTION OF PLATE II.

Two photomicrographs of intestinal villi of rabbit, forming companion representations to those given on Plate I, to description of which refer. Magnified 120 diameters.

FIG. 3.—Longitudinal section.

FIG. 4.—Transverse section.

PLATE II.

FIG. 3.

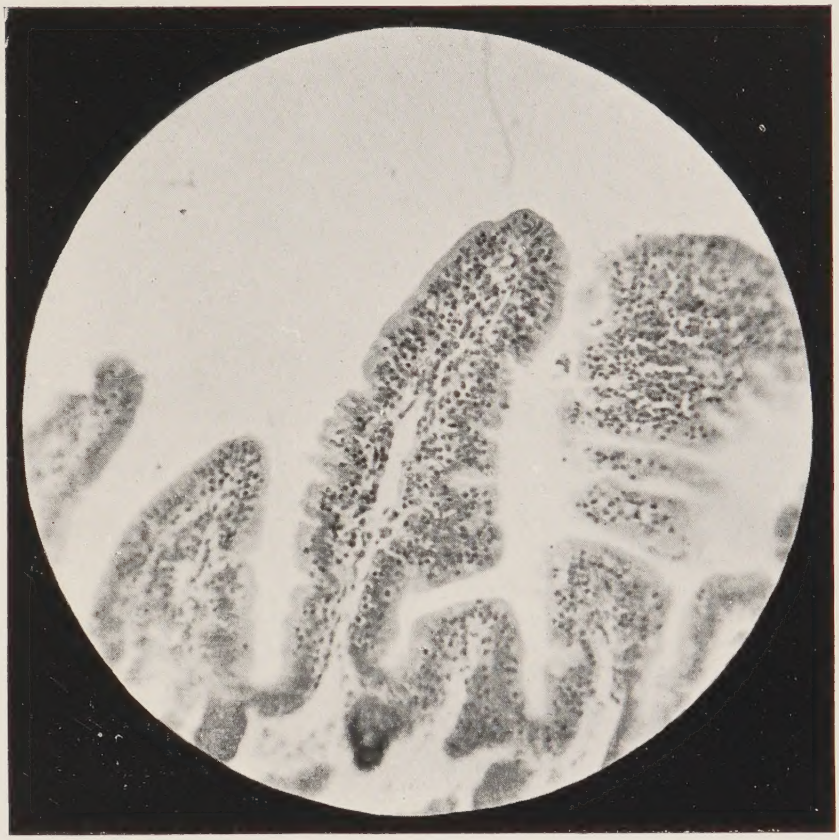
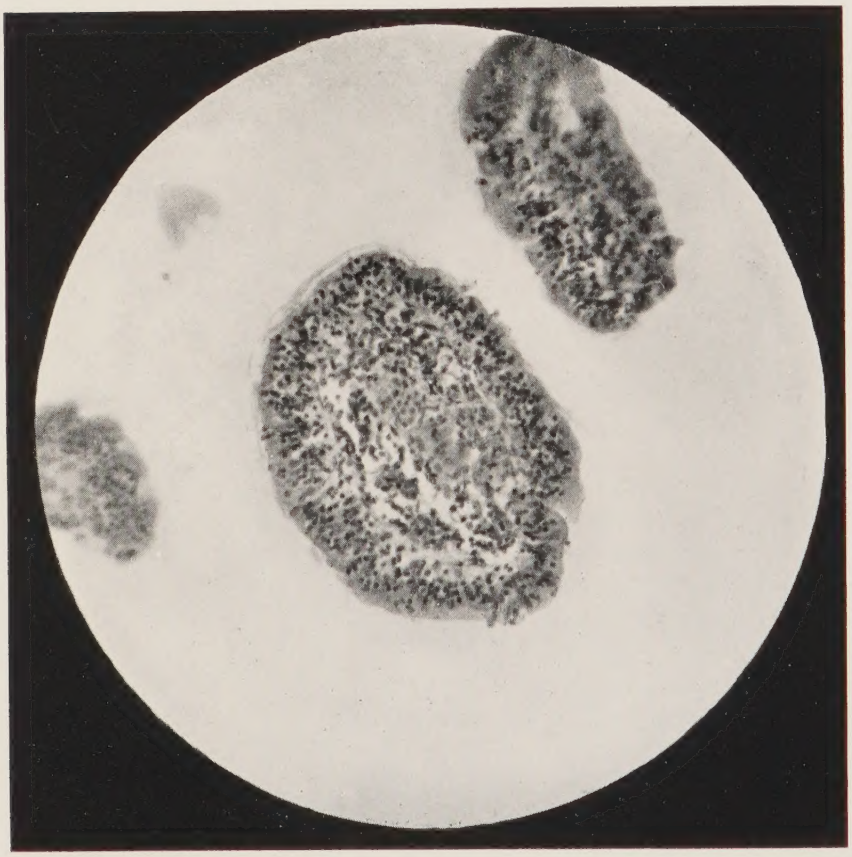


FIG. 4.



Lymphocytes in intestinal villi.

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DESCRIPTION OF PLATE III.

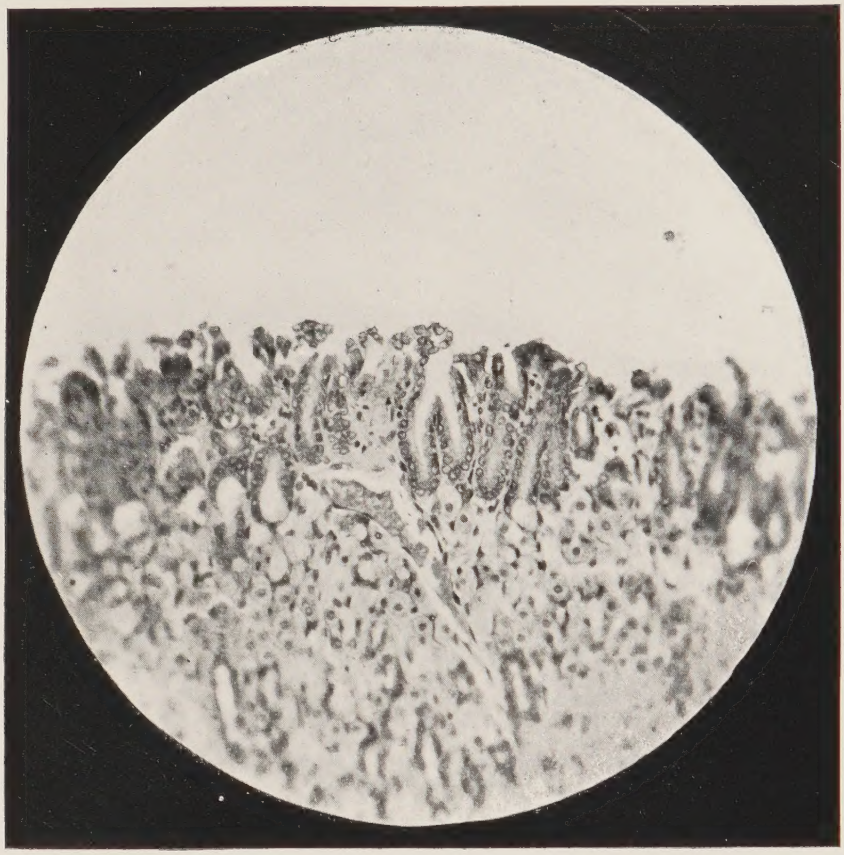
Photomicrographs of sections of the mucous membrane of the stomach and large intestine of the rabbit prepared in the same manner as the sections of the villi. They are supplied for the sake of showing the contrast existing with the villi. Magnified 120 diameters.

Fig. 1.—Section of stomach. Gastric follicles are seen extending to the surface. The majority of the bodies having the appearance of lymphocytes are evidently stained nuclei of cells. Cells with stained nuclei are distinctly visible in many places.

Fig. 2.—Section of large intestine. Lieberkuhn's follicles coursing upwards are seen, and also the superficial columnar epithelium of the intestine. Many or most of the dark bodies visible are manifestly stained cell nuclei.

PLATE III.

FIG. 1.



Mucous membrane of stomach.

FIG. 2.

Mucous membrane of large intestine.

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DESCRIPTION OF PLATE IV.

Photomicrographs of lymphocytes from the lacteal vessels of the rabbit at a period of full digestion. Prepared after the manner adopted for making a dry blood film. Stained with Jenner's eosin-methylene blue. Magnified 170 diameters.

Fig. 1.—Lymphocytes from the vessels between the intestine and the mesenteric glands. Vessels incised near to the glands.

Fig. 2.—Lymphocytes from the vessels between the mesenteric glands and the *receptaculum chyli*.

The lymphocytes shown in Fig. 2 are seen to be larger than those in Fig. 1 ; whatever the explanation, the point of difference is distinctly noticeable in the microscopic examination of the two slides.

In both figures examples of the large and small types of lymphocytes are to be perceived.

PLATE IV.

FIG. 1.

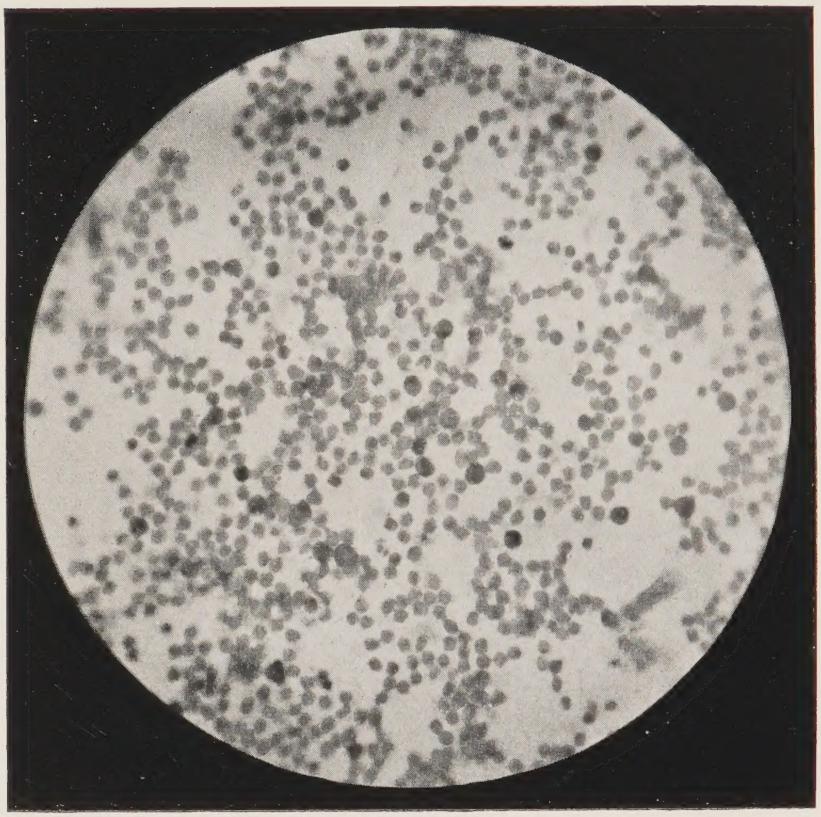
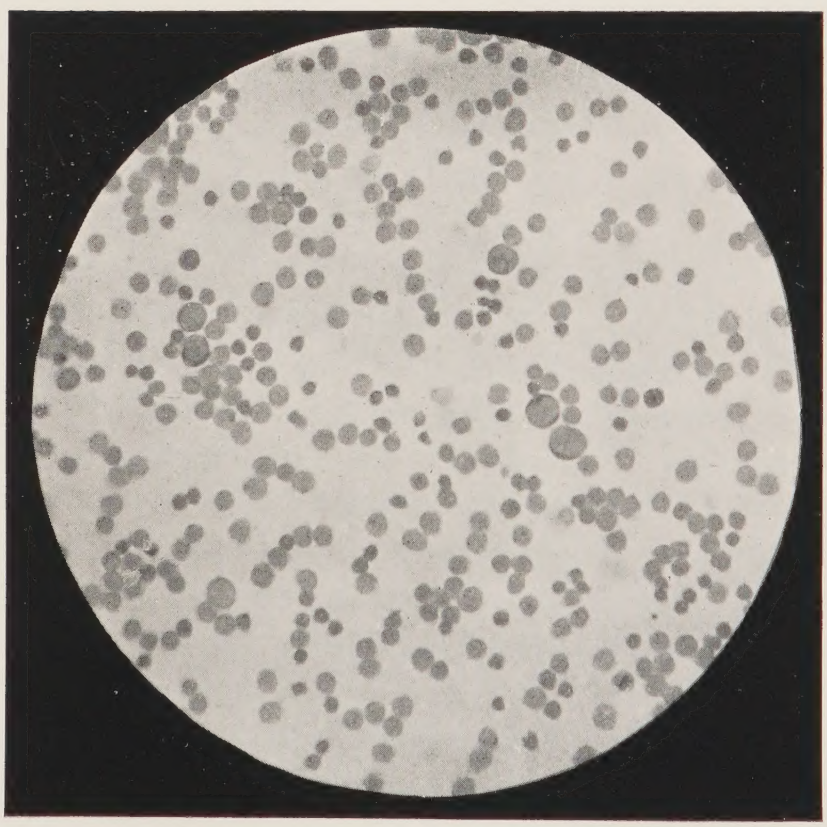


FIG. 2.



Lymphocytes in chyle.

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procedure for obtaining information being necessary, and if such measures have not been adopted there is no wonder that so few lymphocytes have been found, and that persons should have been driven to seek for a means of lymphocyte transport other than through the lacteals.

A 10 per cent. solution of citrate of potash is used to prevent coagulation. The part is moistened with it at the spot where the absorbent vessels are about to be cut through, and it is otherwise used in a befitting manner for securing the attainment of the object in view.

When chyle is thus obtained there is no lack of lymphocytes to be met with on microscopic examination. On Plate IV representations are given from microscopic slides. Fig. 1 is from the fluid collected from the vessels on their way from the intestine to the mesenteric glands. Fig. 2 applies to the contents of vessels that have emerged from the glands. The preparations were made in the same way as blood-film slides, Jenner's stain being the one employed.

With such an illustration, no doubt can be entertained about the passage of proteid through the lacteal vessels. In the figures the lymphocytes seem as thickly congregated as blood-corpuscles on a blood-film slide. Each lymphocyte is the representative of proteid on its way from the alimentary canal to the blood.

Through the medium of blood-counting investigations, it has been ascertained that a conspicuous rise in the number of lymphocytes in the blood occurs at the period of digestion. As is known, the term "digestion lymphocytosis" has been applied to the condition. Authorities, not being alive to what I have pointed out, have been hard pressed to find a source of origin for the lymphocyte increase, and the view—an odd one it certainly seems, looking broadly at the matter—that has met with most favour is that the bone-marrow constitutes the looked-for medium.

With the light that is thrown upon the subject by the recognition of the flow of lymphocytes that takes place through the lacteal system, digestion lymphocytosis becomes an explicable phenomenon. The evidence afforded through the

medium of the villi shows that they constitute a seat of lymphocyte formation and that food is an influencing factor. The mere fact, however, of the presence of lymphocytes in the villi does not constitute the main point to be dealt with in connection with the matter. It is the flow of lymphocytes from them that supplies the evidence of leading importance.

Bearing on this, it is noticeable that in the fully fasting state the absorbent vessels from the intestine are scarcely to be discerned, if they are to be discerned at all. Under these circumstances the kind of result that attends an attempt to collect lymph from them is easily to be conjectured. No absorption from the alimentary canal is going on, and there is nothing to create a flow through the lacteals. More or less complete stasis constitutes, in fact, the condition existing. At a period of digestion, however, the vessels are observed to be in a very different state. No matter whether they happen to be charged with lymph or chyle, they are readily visible, and if snipped through with scissors give exit to a free escape of fluid. It is evident that at this period an active flow is taking place through the vessels in question.

There is no dispute, I think it may be said, upon the point of there being an active flow taking place through the lacteals at the digestion period. It may further be said that it is a matter of general belief that the amount of fluid reaching the blood through them in the twenty-four hours is something considerable. Probably, looking at what has been noticed in connection with cases of injury to the thoracic duct and with cases of chylous discharge from the cutaneous surface, a litre constitutes a low estimate for the human subject. However this may be, it is obvious that the lymphocytes contained in it, as testified by the evidence afforded by the photographic illustrations supplied, must lead to the passage of a large amount of proteid into the blood and render it unnecessary to look for the entrance of proteid from the food through any other channel.

Digestion lymphocytosis, under the view set forth, is the result of the growth of lymphocytes from the digested products of the food, and the growth of lymphocytes in its turn gives

rise to the disappearance of peptone and sugar that is noticed to occur. Everything fits in and gives a consistent completeness.

Assimilation of Carbohydrate by Conversion into Fat.

I dealt with this subject in my *Physiology of the Carbohydrates,* published in 1894, and I will here give a transcript of passages (p. 246, *et seq.*) which set forth what it is desirable should here be stated.

"The fact of the production of fat from carbohydrate is abundantly attested by examples that can be drawn from the higher forms of vegetable organisation, in some of which it is very extensively carried out.

"In the oily seeds the fat is preceded by starch and sugar. Sachs says: 'Before maturity such seeds contain no fat, but only starch and sugar. Such unripe seeds (*e. g.* of pœonia) may be detached from the mother plant, and allowed to lie in moist air with the result that the starch disappears and is replaced by fatty oil.' Again: 'There is not the slightest doubt that fat is formed in ripening seeds from carbohydrates, particularly starch, since this transformation takes place in the nearly ripe seed, even when taken out of the fruit, when no other material is available under the circumstances for the formation of fat.'

"If, as appears in the oily seeds, it is susceptible of demonstration that fat is produced from carbohydrates, it is equally demonstrable that carbohydrates are reciprocally producible from fat. The embryo of the oily seed grows in the same manner, and in its growth develops the same kind of structure as that of the starchy seed. The cellulose and other carbohydrates found in the seedling are obviously derived from the fatty reserve in the one case, just as they are derived from the starchy reserve in the other.

"However inexplicable, from a strictly chemical point of view, such transformations may be, the fact is evident that in the oily seeds fatty matter is, in the first instance, produced from carbohydrate, and subsequently, in the growth of the seedling, reconverted into carbohydrate.

"In the animal kingdom fat is, without question, produced upon a very extensive scale from the carbohydrates. The animal system constitutes, in fact, a laboratory wherein the capacity exists for converting carbohydrate matter into fat. In the milch cow, in the fattening of animals for the table, and in the production of the *fois gras* in the Strassburg goose, we have instances of the extensive operation of the process, and I need not dwell further upon the question of fact, but will proceed to consider that of where and how the change is brought about.

"The ferments of the digestive system place the carbohydrate matter of our food in a soluble state, if not already existing so. The small intestine is the part of the alimentary tract where absorption of the nutrient matter specially occurs, and here the carbohydrate is intimately intermixed with the product of digestion of nitrogenous matter. Thus prepared, the carbohydrate product falls, in the process of absorption, within the sphere of influence of living protoplasm represented by the cells investing the villi. These cells are recognised as the agents concerned in the absorption of fat, but no thought appears to have been given to them as transformers of carbohydrate into fat, although, if we bestow attention on the matter, evidence is seen to be forthcoming suggesting that they, in reality, fulfil this function.

"It is well known that after food rich in fatty matter the lacteals are filled with milky chyle, that the cells of the villi are more or less loaded with fat, and that fat globules pass from these cells through the centre of the villus to reach the current in the lacteal system.

"Observation conducted upon the vegetable feeder after the ingestion of food rich in carbohydrate matter and poor in fat reveals the existence of a precisely similar state of things. On taking, for instance, a rabbit about four hours after a meal of oats, killing it, and opening the abdomen, coils of the small intestine are seen, especially after a few minutes' exposure, to present a white, opaque appearance, with milky streaks or lines upon the surface, due to flow of chyle beneath the peritoneum; and the lacteals of the mesentery, owing to

the milky character of their contents, are conspicuously visible. The receptaculum chyli is also, from the same cause, readily perceptible, and, if cut into, gives exit to a strongly milky fluid. On the intestine being laid open a more or less densely white condition of the internal surface presents itself to view, due to the extent to which the mucous membrane is charged with fat, and the villi stand out as opaque projections.

"In order that the condition described may be satisfactorily visible it is necessary that favourable circumstances should exist. The animal itself must be in a good healthy state. The food must be of a natural kind and sufficiently rich in farinaceous constituents. Moistened oats, in the case of rabbits, have yielded the most marked results. After fasting, with unfavourable food, and in ill-conditioned animals, the appearance strikingly differs. The intestine is transparent and watery, and the lacteals are not perceptible. Between this condition and that in which the lacteals are fully injected any intermediate degree of milky character may, of course, be perceptible.

"From the appearances presented, then, to the naked eye, it is learnt that under suitable food, rich in starchy matter, the same passage of fat through the lacteals occurs as after feeding directly with fat. It seems to me impossible that the quantity of fat observed to be thus entering the system could be derived from that contained in a free state in the food. Analysis of the oats consumed in my experiments placed the amount of fat present at 5 per cent., which agrees with the estimations made by others.

"Upon the facts before us the following train of reasoning may, I am of opinion, be legitimately set forth. We know upon irrefutable grounds that the capacity of producing fat from carbohydrate matter exists within the animal system, and must be extensively in operation. The intestine constitutes the main seat of preparation of carbohydrate matter for absorption and subsequent utilisation, and from the intestine we find fatty matter flowing into the system through the lacteals, which cannot be adequately accounted for except on the hypothesis of its origin from the carbohydrate matter of

the food. Indisputably, the formation of fat takes place somewhere in the system, and there is no situation more propitiously circumstanced to meet all the requirements of the problem than the intestinal villi. Moreover, with the seat of formation in this position the introduction of fat into the system as a production from carbohydrate food is brought into conformity with its direct introduction—pre-formed from without. In the one case the fat is simply absorbed and reaches the lacteals; in the other it is produced by assimilation from carbohydrate matter, and then similarly reaches the lacteals.

"If we now pursue the matter further, and give attention to the villi, it will be seen that support is afforded to the view that has been advanced.

"It may be confidently assumed that it is through the operation of protoplasmic action that the transformation is effected. For many years I have been acquainted with the fact that the lacteals are well charged, as above described, with milky chyle after the ingestion of carbohydrate food; but it did not occur to me, until recently, that it was permissible to look to the villi as constituting the seat of the production of fat from carbohydrate matter.

"The protoplasm of the cells of the villi may be regarded as specially intended for the performance of assimilative action. If we study the villi microscopically, the appearances seen after the ingestion of food and at a period of fasting are very different. In the fasting state they are covered with a layer of closely-set columnar cells provided with nuclei and granular contents. Here and there cells may be discovered containing a few fat particles, but nothing beyond this in the direction of fat is discernible [the appearance presented by the cells is delineated in fig. 1, Plate V]. At a period of digestion numbers of cells become more or less loaded with fat [as shown in fig. 2, Plate V]. Of those which become thus charged many present a much altered form. The columnar character, it is true, predominates, but the columns are thicker and shorter. Often the cells are conical or pear-shaped. Sometimes they are spheroidal, looking in this state

DESCRIPTION OF PLATE V.

Photo-engravings from pencil sketches of the epithelial cells of the small intestine of the rabbit at a period of fasting and of digestion, reproduced from my work on *The Physiology of the Carbohydrates*, 1894.

Pencil sketches were employed in default of having been able to obtain satisfactory photomicrographs owing to the slight shade of difference existing between the cells and the surrounding ground. They may, however, be taken as faithfully representing the typical distinguishing characters belonging to the fasting and full digestion periods.

In order to obtain the cells in a disjoined state the intestine, after removal from the animal, is allowed to remain for a few hours previous to being opened. In this way they become detached and separated by the solvent action of the secretion, and by lightly scraping may be removed from the surface. Immersion of the piece of intestine in 0·1 per cent. solution of formalin serves to enable it to be preserved for a time from further change.

Fig. 1.—Represents the cells in the fasting state. They are of a typically columnar character and devoid of visible fat, except that here and there a cell may be seen with a few fat globules in it.

Fig. 2.—Gives a representation of a collection of the characteristic fatty cells to be seen at a period of full digestion after a meal of oats. The modification of form assumed by many of the cells is a very striking phenomenon, and the delineation supplied gives no exaggerated idea of the extent of modified form that may here and there be seen. That these modified cells do in reality consist of changed epithelium may, I think, be taken as shown by the intermediate stages that are perceptible, and by the fact that the distinctive "striated border" appertaining to the epithelial cells is often unmistakably visible.

PLATE V.

FIG. 1.

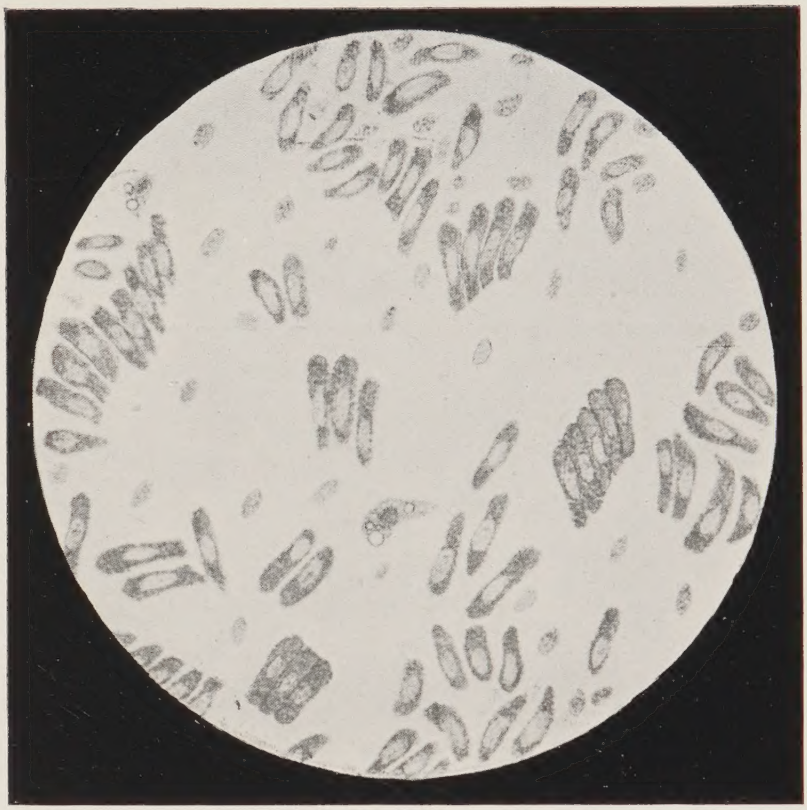

Photo-engraving from sketch showing appearances presented by cells of villi from a fasting rabbit.

FIG. 2.

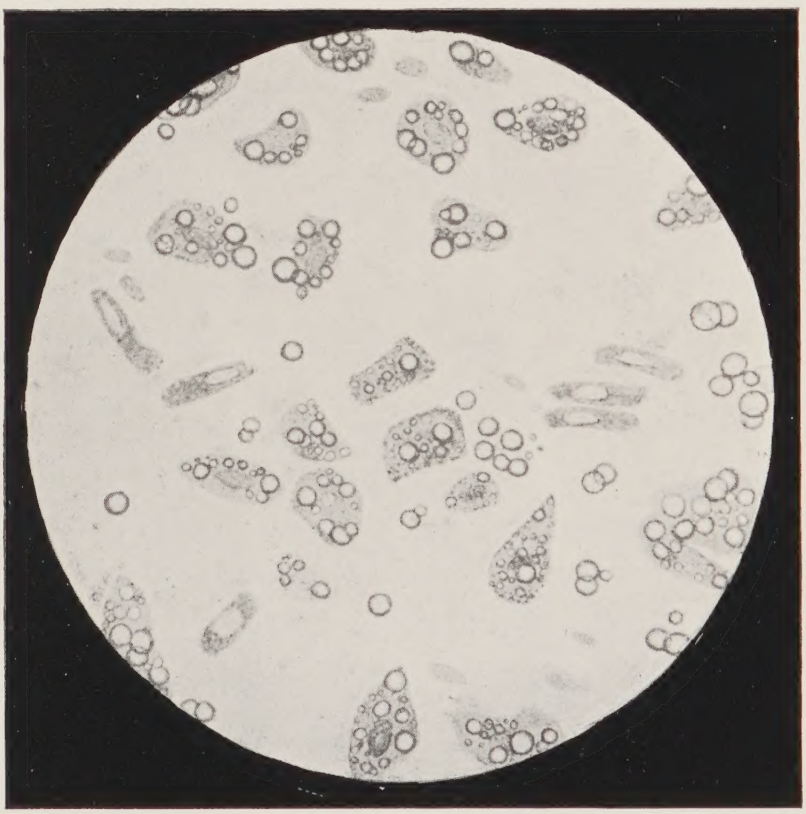

Photo-engraving from sketch showing appearances presented by cells of villi from a rabbit killed four hours after having been fed with oats.

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very much like fat-containing cells derived from the liver. Speaking of this resemblance, the cells of the liver, indeed, appear to play a supplementary part in the formation of fat from carbohydrate to that played by the cells of the villi, assimilating the carbohydrate matter which escapes being assimilated in the villi, and which, as a result, is permitted to reach the portal blood. It is interesting to notice that both in the case of the lacteal and the vascular system a second line of protoplasmic matter, consisting of the lymph-cells of the absorbent glands on the one hand, and the cells of the liver on the other, has to be passed before the general circulation is arrived at.

"I do not see that any other conclusion is permissible than that in the cells depicted from villi of the rabbit fed upon oats the fatty matter was the product of the influence of protoplasm upon the carbohydrate matter ingested. Looked at in their entirety, the points before us stand thus. Beyond all question, as previously stated, the production of fat largely takes place within the animal system from carbohydrate. After carbohydrate food the lacteals are seen to be charged with milky chyle in the same manner as occurs after the direct ingestion of fat. The protoplasmic cells of the villi intervene between the carbohydrate material contained in the alimentary canal and fatty chyle contained in the lacteals. These protoplasmic cells, in the presence of carbohydrate food, are found to become more or less loaded with fat, which finds its way into the lacteal system. Within the villus there is evidently a great protoplasm-generating capacity. Besides the columnar epithelial layer, which, as I have before mentioned, at the time of assimilative activity assumes, to a greater or less extent, an altered character, a number of lymph- or wandering-cells are to be seen. The two lie in close juxtaposition, and probably both contribute towards rendering the villi richly provided with protoplasm, propitiously placed for exerting an assimilative action on the food principles prepared by digestion for service in the system.

"The cells of the liver, as I have intimated, probably supplement those of the villi in producing fat from the

carbohydrate which escapes disposal in the villi and reaches the portal vein as sugar. If this be the case, we ought to find in the process of fattening with carbohydrate food that the liver gives evidence of being involved to a greater extent in the operation in question, where the villi and lacteal system are less perfectly developed than under the opposite condition. Now, this happens to accord with what is actually observed. In the bird the villi are much less highly developed than they are in the mammal, and in the process of fattening (for the production of *fois gras*) to which the Strassburg geese are subjected, the liver, as is known, attains enormous size from the deposition of fat. In the mammal the case stands otherwise. Many years ago I visited the slaughter-houses to which some of the fat animals exhibited at the Christmas London Cattle Show were taken, and was struck with the healthy and fleshy-looking state of the liver and other abdominal organs. With efficiency on the part of the villi the liver would escape the tax of work that under other circumstances would be thrown upon it."

Practically little or no attention has been given to what was thus brought forward in my *Physiology of the Carbohydrates* on the subject of the production of fat within the epithelial cells of the villi from the carbohydrate of the food. The sum and substance of my work was assailed by a physiologist who had just before committed himself to a proposition based upon experimental results that could have no validity if my position was left undisturbed. The experimental results in question were afterwards acknowledged to be faulty, but the allegations connected with the point under consideration that were made in the criticism of my work have deterred physiologists from giving the consideration to the matter that I am firmly of opinion it merits. It is not to be conceived that the mere administration of carbohydrate food to an animal will of necessity give rise to the epithelial cells becoming charged with fat globules. The issue is dependent upon bioplasmic action, and, for the due exercise

DESCRIPTION OF PLATE VI.

Reproduced photo-engraving from my work on *The Physiology of the Carbohydrates* of a photomicrograph of a section of the villi of a fasting rabbit.

The intestine was treated in the usual way for fat, staining with osmic acid, and then imbedded in paraffin for section-cutting. Preparatory to mounting in Canada balsam it was faintly tinted with hæmatoxylin.

No sign of the presence of fat is perceptible. Magnified 100 diameters.

PLATE VI.

Villi of fasting rabbit showing absence of fat.

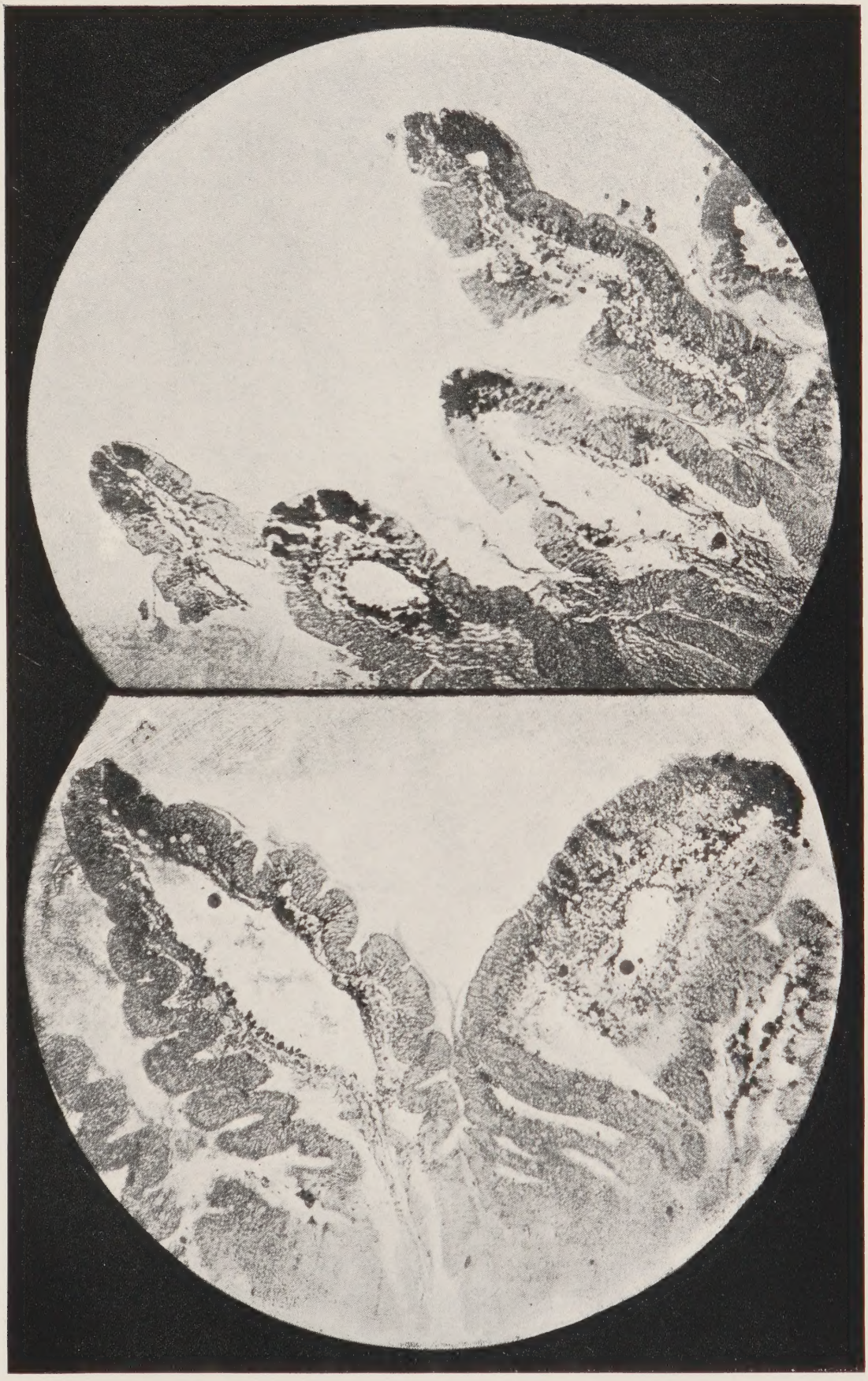
Adlard & Son, Impr.

DESCRIPTION OF PLATE VII.

Reproduced photo-engraving from my work on *The Physiology of the Carbohydrates* of photomicrographs of sections of the villi of a rabbit killed four hours after having been fed with oats.

The preparation was dealt with in the same manner as that belonging to Plate VI. As a result the osmic acid staining has brought into view a large quantity of fat. Magnified 100 diameters.

PLATE VII.



Villi of rabbit after being fed with oats, showing presence of fat.

Adlard & Son, Impr.

DESCRIPTION OF PLATE VIII.

Photo-engraving of photomicrographs of two recently prepared sections of villi of the rabbit. The specimens were treated with an osmic acid fluid and otherwise prepared after the usual manner

FIG. 1.—Villi from a fasting rabbit. No sign of the presence of fat.

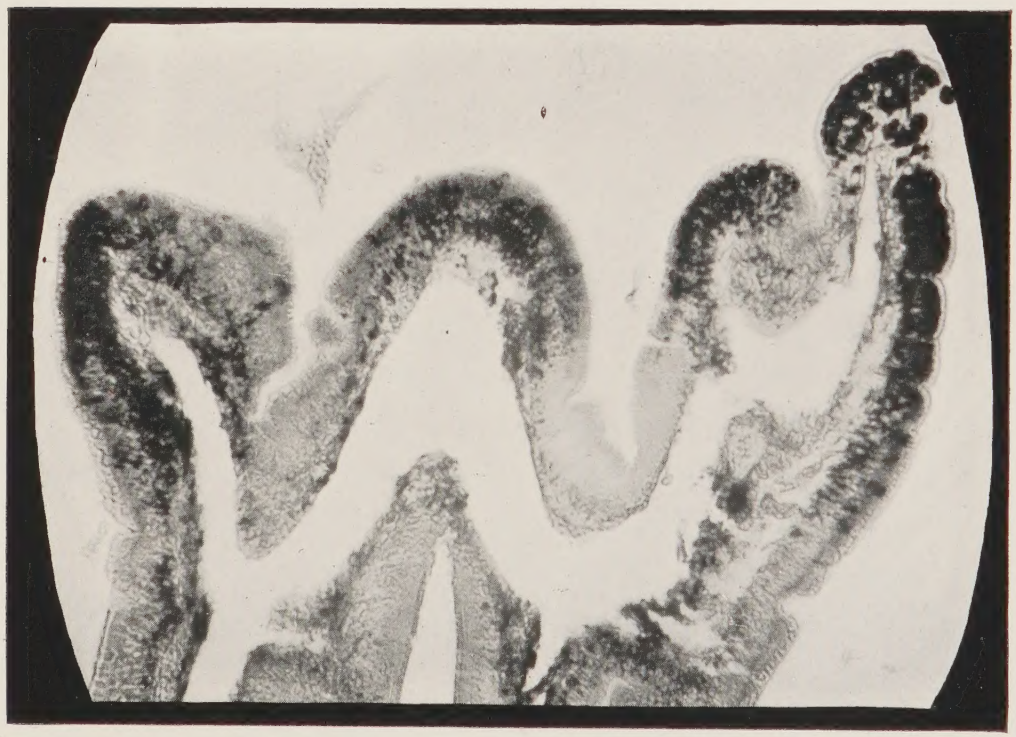
FIG. 2.—Villi of a rabbit at a period of full digestion after being fed on oats. The engraving shows the presence of an abundance of fat.

PLATE VIII.

FIG. 1.

Villi of fasting rabbit, showing absence of fat.

FIG. 2.



Villi of rabbit after being fed with oats, showing presence of fat.

Adlard & Son, Impr.

of this, not only must the food be of a natural kind, with the constituents present in proper proportion, but natural internal conditions must also prevail. No matter what the amount of carbohydrate given, if the conditions within are not of a propitious nature no fattening effect (formation of fat must take precedence) can be expected to be produced.

It was suggested that the fat met with in the lacteals and the villi came from the 5 per cent. of fat contained in the oats. To this I would say that I have in some instances seen the lacteals so filled with a good milky chyle, the outside surface of the intestine so streaked with milky lines due to the presence of chyle in the lymph-spaces beneath the peritoneum, and the mucous membrane so conspicuously white from the presence of fat in the villi, as to render it impossible to conceive that the 5 per cent. of fat in the oats could for a moment be credited with the capability of producing such a state of things. The appearance has been pretty nearly equal to what is visible in the cat and dog after a meal of food rich in fat. It is to be remarked that only from time to time are such instances as I have depicted come across, and this renders the result less likely to be due to ready-formed fat present in the food. Much variation is found to exist in connection with the matter, and it is impossible to secure that intestinal activity shall be thrown into play as may be desired.

Plates VI, VII, and VIII furnish photo-engravings of photo-micrographs of sections of osmic acid stained intestinal villi of the rabbit, taken respectively at a period of fasting and of full digestion after feeding with oats. The sections, it is noticeable, in the case of the fasting animal show no appearance of fat, whilst those derived from the fed animals display its presence in abundance. Not only is black-stained fat visible in the substance of the epithelial layer, but particles can be made out coursing along within the centre of the villus. The same channel-like appearance is perceptible in the centre of the villus that was commented upon as being perceptible when I was dealing with the transit of the lymphocytes.

THE FUNDAMENTAL PRINCIPLES, AND THE TREATMENT, OF DIABETES DIALECTICALLY DISCUSSED.

In the case of the healthy person, it is noticeable that carbohydrate food is taken and all that is afterwards observed is that it is disposed of within the system in a manner to prove beneficial to the economy. In the case of the diabetic, the result that follows is of an opposite nature. Instead of being disposed of in a manner to prove beneficial, the carbohydrate taken passes in an unutilised state through the system, and escapes with the urine in the form of sugar. In the one case it is obvious that a certain action must occur to lead to the result that is witnessed. In the other it is equally obvious that this action must fail to take place. There is action on the one side, and failure of action on the other, to be dealt with, and, in seeking for a right understanding of the *rationale* of the latter, it is necessary to have a preliminary right understanding of that of the former.

Such is the position in which the circumstances connected with diabetes stand. Unless we are on a right basis with regard to the natural course of events, we are not likely to be entitled to consider that we can possibly possess a right comprehension of the faulty state underlying diabetes.

The contents of the preceding pages have shown that the views on glycogenesis held by physiologists do not stand the test of experimental examination. Unfortunately, they are

still permitted to influence the mind in connection with diabetes, although they are manifestly irreconcilable with the facts belonging to the disease. The teaching, indeed, founded upon the glycogenic doctrine, that is applied to the physiological state, implies of itself the production of the diabetic state. It is taught that there is a functional transport of sugar from the seat of absorption and from the liver, through the circulatory system, to the seat of utilisation in the tissues. The effect of such transport could not be otherwise than the production of glycosuria.

Sugar is a small molecular body, and, like other small molecular bodies, as urea, salts, etc., escapes from the system with the water of the urine proportionately to the amount reaching the blood. There is no longer any question about the invariable presence of sugar in healthy urine, and the results recorded in the preceding pages show that it is present to a considerably more notable extent than, I believe, is generally conceived. Fehling's test, owing to the other constituents of the urine, does not, under ordinary circumstances, give any indication of its presence. It is thereby not surprising that an erroneous notion should have been produced. With the employment of the ammoniated cupric test, however, not only is its presence most readily disclosed, but likewise its quantity most easily estimated, and by determining the cupric oxide reducing power before and after hydrolysis, the character of the sugar is susceptible of being defined.

Sugar, then, is always being carried, in company with the urinary water, out of the system from the blood, apart from any consideration of functional connection with the food. Let it now be supposed that a functional transport of sugar from the food to the tissues is taking place, and, upon this supposition, let us ask ourselves what effect on the urine must be expected to follow.

Experiments on the direct injection of sugar into the circulation help us materially in answering the question, and it has to be stated that the results obtained afford evidence of an outflow of sugar standing in proportionate relation to the sugar injected. With the injection of large quantities of

sugar a diuretic effect is produced, and there is sure to be a large output of sugar. When small quantities, however, are employed, although distinct evidence of output exists, yet, owing to modifying circumstances, the result may not be as decisive in some instances as it is in others. For instance, it may happen that the kidney may be at the time, from the collateral conditions existing, in a more or less inactive state, and naturally without the flow of urine there would not be the output of sugar. When, however, the occurrence of a flow of urine is taking place, an escape of sugar may be looked for in the case of small quantities as well as large, according to the extent to which sugar has been present in the blood.

To be permissible for the urine to remain unaffected by the entry of sugar into the circulation it would be necessary for an immediate disappearance of it to occur so as to prevent the kidney being reached. Experimental observation shows that this does not in reality happen. It is true that, after introduction into the circulation, sugar does, in the course of time, become assimilated and lost sight of, but meanwhile it is continuously flowing through the vessels of the kidney, and, as a result, being eliminated with the urine.

A striking analogy can be traced between peptone and sugar with respect to their capacities for being assimilated. Both are seen to be assimilated with the greatest facility and rapidity when viewed in connection with the natural position they hold as food principles in transit from the alimentary canal to the blood. So perfectly is their assimilation here carried out that neither gives evidence of reaching the general circulation and thence, *a fortiori,* the urine. Introduced in a direct manner, however, into the circulatory system, they both fail to be immediately assimilated. It is only after the lapse of a certain amount of time that they are found to have disappeared, and in the meantime they have both been flowing off with the urine.

It cannot be otherwise taken than that sugar stands in the same position as any other small molecular body in relation to the kidney, and flows off with the urine proportionately to

the extent to which it exists within the circulatory system, whether the quantity be large or small. The question of quantity assuredly cannot be reasonably expected to constitute a factor for determining whether there shall be an escape of sugar or not.

Experience in every direction shows that there is no such thing as the sometimes talked of impermeability of the kidney to sugar. Whatever sugar reaches the circulation becomes revealed through the medium of the urine. Under natural circumstances the urine gives no indication of the production of any effect upon it by the ingestion of food, but if sugar passed as free sugar into the circulation from the food it may be considered that the urine could not fail to afford a revelation of the fact. In diabetes, sugar reaches the urine from the food. It does so as a consequence of its reaching the blood, and if it similarly reached the blood in health it would similarly reach the urine and cause glycosuria to rank as the ordinary condition.

If it is contended that sugar reaches the blood from the food to be conveyed as such to the tissues for assimilation and utilisation, proof should be forthcoming, in view of the fact that there is no immediate disposal of sugar that reaches the circulation, that the water of the blood can pass off within the kidney without carrying with it the sugar present in a state of solution.

I have spoken of the effect resulting from sugar being allowed to reach the circulation from the food. The remarks which have been made apply with equal force to sugar derived from any other source. Hence, if free sugar reached the circulation from the liver, as is contended for under the glycogenic doctrine, the urine would be influenced in proportion as it did so. There can be no doubt that the glycogen of the liver contributes to usefulness in the economy, but its transit to the seat of utilisation must not take place in the form of free sugar. The matter has been already dealt with in its appropriate place in a preceding part of this volume.

Much assistance is afforded in unravelling the problem of the metabolism of carbohydrate by what is observed in con-

nection with diabetes, and physiologists, through failing to be brought into contact with the disease, are deprived of the advantage to be thus derived. Now, in this disease experience demonstrates in an incontestable manner that there is the closest relationship between the carbohydrate ingested with the food and the sugar eliminated with the urine. The food which, in a state of health, produces no effect upon the urine leads, in diabetes, to an elimination of sugar in proportion to the amount of carbohydrate present. Such, it may be considered, would also be the case in the healthy state if the carbohydrate of the food passed as free sugar into the circulatory system.

The eliminated sugar derived from the food in diabetes arises from sugar having been permitted to reach the circulation through faulty assimilative action. If the carbohydrate is assimilated, and thereby does not reach the general circulation in the form of sugar, there is nothing to lead to the elimination of sugar with the urine.

The assimilative power is the basal point in connection with diabetes, and this assimilative power is not unlimited in a state of health. It is a well-known fact that with everyone the urine may be rendered saccharine by the ingestion of sugar in large amount. In these circumstances the assimilative power is overstepped, and, as a consequence, sugar reaches the circulatory system and thence the urine.

Alimentary diabetes is simply due either to a loss or to an impairment of this assimilative power. With respect to impairment of the power, an infinite variability of extent is found to exist in different cases. In some the impairment is so slight that it is only when carbohydrate is taken in full amount that sugar finds its way into the urine. At other times the urine is in a normal condition. Between this condition and a complete loss of power any intermediate stage may be met with. For each case an assimilative power exists which is special to it, and in all cases it is found that, as long as the carbohydrate ingested is within the power of assimilation existing, there is no wrong state of urine discoverable. Immediately, however, the carbohydrate stands in excess of

the assimilative power, that which is in excess and has failed to be assimilated reaches the circulatory system as sugar, and thence, as sugar, flows off as waste material with the urine.

We have in these cases to deal with a simple alternative. If the carbohydrate is within the assimilative power that may happen to exist, it goes to the good of the system, and does not affect the urine. If, on the other hand, it exceeds the assimilative power, it passes off as sugar in the urine in proportion to the extent to which the assimilative power has been exceeded.

There is a wonderful precision noticeable in connection with what has been spoken of. The amount of carbohydrate that can be taken without rendering the urine saccharine is very sharply defined. It is, indeed, almost incredible the certitude with which even only a slight overstepping of the boundary line will tell upon the urine. For sugar, it is to be remarked, there is a less tolerating capacity than for starch. In this there is nothing surprising, seeing that sugar is in a suitable state for immediate absorption, whilst starch having to undergo digestion, which is a gradual process, absorption of sugar from it can only occur in a gradual manner, and, obviously, gradual absorption must be more favourable than rapid absorption for the effective exercise of assimilation.

It is possible for the assimilative power to exist in a perfectly steady state for a lengthened period—by which I mean sometimes for years, or it may be indefinitely—if, by adjusting the carbohydrate to the power of assimilation existing, the urine is kept free from the abnormal presence of sugar, which implies that the system is being kept in a normal state.

A diabetic, when thus circumstanced, is virtually in the position of a healthy person, with the sole exception that his assimilative power over carbohydrate has become reduced to a lower level than that belonging to the normal state. He exhibits no signs of ill health, and his abnormality is only discoverable by testing his capability of disposing in a proper manner of carbohydrate food. By a test-meal of carbohydrate the urine is made to reveal the state existing, and

through the amount of carbohydrate that can be taken without leading to the passage of sugar a measure is given of the extent of impairment of assimilative power to be dealt with. The effect upon the urine follows at once, and, where sugar has entered into the test-meal, an hour or so may suffice for sugar to be distinctly recognisable in the urine. This stands in accord with what would be expected. Assimilation takes place coincidently with absorption, and, when not complete, sugar is permitted to reach the general circulation, and thence straightway passes into the urine.

The position of things is, indeed, identical with that arising from the direct introduction of sugar, by injection, into the circulation. With a moment's reflection, it will be apparent that it could scarcely be otherwise. It can make no difference as regards the route by which the sugar reaches the circulation, and what is noticeable is that whilst the carbohydrate can be freely ingested under healthy conditions without showing itself in the urine, its ingestion in diabetes is followed by the passage of sugar into the urine in an analogous manner to that occurring in association with the direct injection of sugar into the circulatory system.

The features of a case of "alimentary diabetes" are dependent on the extent of impairment of assimilative power over carbohydrate that happens to exist, and this is grounded on the inherent characters of the case and on the manner in which the case is dealt with. It is sometimes found that the loss of assimilative power sets in more or less suddenly and severely, giving a sharp onset to the disease. Frequently, however, the loss occurs gradually, and then there is a small beginning to start with, followed by subsequent growth of the condition at different rates of progression. At first the impairment of power may not be sufficient to give rise to any significant elimination of sugar, the greater portion of the carbohydrate taken being within the assimilative power existing. During this stage, there being no symptoms to excite suspicion of anything wrong existing, the case runs on undiscovered, unless it may by chance happen that the urine is examined for life assurance, or some other purpose, when

the presence of sugar is brought to light. Should the sugar not be revealed in this way the condition will continue to grow until sufficiently pronounced symptoms are produced to lead to its recognition. After recognition, it is common for circumstances which had not previously elicited attention to be brought to mind, and thus show that the malady must have been for perhaps a considerable time existing.

The sketch given supplies a representation of what is commonly noticed in connection with the setting in of the diabetes. Left alone, as perforce happens previous to the disease becoming recognised, the wrong condition is fed by, and grows upon, itself. The growth, however, takes place at a very varying rate in different cases. Sometimes when the case presents itself there are positive grounds for showing (the urine having been examined for some object or other, unconnected with the question of diabetes, at a particular period) that the disease can only have been of short duration. Sometimes, on the other hand, upon equally positive grounds, it may be concluded that the progress has been running on for some few years. It is known that urine containing sugar leaves white spots that are difficult to brush out on articles of wearing apparel. Now, with reference to this point, I have come across instances where the patient, to his annoyance, has been noticing these spots, without being aware of their meaning, for a considerable time, and where even they have been found upon trousers that may happen to have been put by and not worn for a few years previous to the recognition of the existence of the complaint. An incident of this kind indubitably denotes that the disease existed a long time prior to when it was discovered, and testifies to the slow progress of the failing assimilative power that may be made. I may remark that it is especially in cases where there is an underlying family history of the disease that this kind of event is most likely to be observed.

The growth of the disease that I have outlined as taking place before any measures of treatment are adopted may be confidently looked upon as in great part due to the effect of the sugar which has been permitted to traverse the system as

a result of defect of the assimilative power over the carbohydrate of the food. With the growing defect, less and less of the carbohydrate taken has been assimilated, and concomitantly more and more sugar has traversed the system to the urine, and thus progressively intensified the condition. The transit of sugar through the circulation from the food to the urine throws the system into an abnormal state, and the greater the abnormal state the greater the ill effects produced. Leave the abnormal transit of sugar untouched and nothing can avert an unfavourable onward march of the disease.

The only means of rectifying matters is by combating the abnormal state, and bringing about an amendment with respect to the sugar which is exerting a pernicious action upon the system; and it is only by the agency of food that this can be done. As long as carbohydrate is being taken which fails to be assimilated, and to be thus prevented reaching the circulation, so long will sugar be proportionately passing off with the urine. If the power does not exist to perform the assimilative work, the work cannot be performed. This is an obvious truism.

The point, then, in the circumstances being dealt with, is that a demand for assimilative work is created by the food that is being taken, and that the power is wanting to meet the demand. As a result, the system is being oppressed with sugar, which flows off from it with the urine in proportion as it flows in. Suppose, now, the demand is removed by the withdrawal of carbohydrate from the food administered. It is not difficult to see the result that should follow, and experience confirms the prediction to be made.

The effect is immediate and most marked. In some cases, especially those in which the disease is only of recent onset, twenty-four or forty-eight hours may suffice for the removal of the sugar from the urine. In those which have been allowed to become established the sugar does not so quickly disappear, but in many of them, if steady perseverance be given to the required dietetic measures, the sugar is found after the initial drop to become less and less, and then in a

couple or three weeks to disappear. In severe, thoroughly established cases the power may not exist to effect a removal of the sugar. These constitute the bad cases, the cases which, as a rule, drift on from bad to worse, until a fatal termination ensues.

It may be stated in connection with what has preceded that in diabetes we have a very multiform kind of disease to deal with. It is well known that age is an all-important item of consideration. The prospect in young subjects is very different from that in persons of more advanced years. Whatever may later on prove to be capable of being said, at present it must be stated that in the former group of cases we have a much more formidable condition to deal with than in the latter. More or less rapid progressiveness, in spite of all measures that may be adopted, is the characteristic feature of the one group as compared with the other.

What is recognised as representing the classical type of the disease occurs especially in persons below the middle period of life. There is as much of a progressive nature belonging to it as is noticeable in progressive muscular atrophy, locomotor ataxia, paralysis of the insane, etc.

It is true the rate of progress varies. In some cases, particularly in those of a hereditary nature, the progress, when the patient is placed under favourable conditions, is sufficiently slow to permit of life being prolonged for a considerable number of years. In practically all cases it is found that the disease is amenable to dietetic treatment at the beginning in a manner that it is not later on. Although it may be predicted that a bad prospect is ahead, yet at the beginning the case ordinarily yields to dietetic management in the same way as an ordinary case of the "alimentary" type.

It is virtually at the time a case of "alimentary" diabetes, and there may possibly exist a certain amount of assimilative power over carbohydrate, a state of things that renders the supply of carbohydrate that can be assimilated—in other words, that can be taken without throwing sugar into the urine—necessary for keeping the patient in a satisfactory condition. False hopes are apt to become engendered, for to all

appearances the health has become restored, but sooner or later, notwithstanding steady persistence in the treatment, the urine can no longer be maintained in a sugar-free state.

An insidious "something" has been advancing within, and now a new type is found to be assumed by the disease. Not only have we to deal with the condition that has pre-existed, but something further presents itself to add to the trouble. The tissues begin to undergo a wrong retrograde metamorphosis. Instead of katabolism proceeding in a normal manner and leading to the generation of the normal final products, accompanied with the output of energy arising therefrom, as the issue, it, by virtue of the agency of an abnormal influence in operation, is made to stop short of this result. As a consequence sugar is cleaved off which, passing into the circulation, flows out with the urine, carrying with it unutilised energy.

When this condition is reached there is a twofold source for the eliminated sugar. There exists both a faulty assimilation or building up, and a faulty katabolism or breaking down, each of which gives issue to the contamination of the circulation with sugar. The eliminated sugar still remains under the direct influence of the carbohydrate matter that may happen to be taken, but it is no longer capable of being controlled by the instrumentality of food as before. Carbohydrate food may be withheld and still the elimination proceeds, but not, of course, to the same extent as when sugar was being derived from the twofold source.

Sugar is not the only principle derived from the wrong katabolic or breaking-down process in operation. There are others—the acetone series of products—which likewise make their appearance, and which, like the sugar, are cast out of the system with the urine. β-Oxybutyric acid, diacetic acid, and acetone are the products referred to. Each contains, and therefore carries off, unutilised energy. No wonder can be entertained, in view of this superadded waste, at the active loss of weight that occurs when the "alimentary" passes into the "composite" form of diabetes, if the condition characterising the latter should exist to any pronounced extent.

Another source of evil, however, attending the production of these principles is that the acids belonging to the group act perniciously on the blood by appropriating its sodic alkali, and thus interfering with the transport of carbonic acid from the tissues to the lungs. To this condition the term "acidosis" has been applied, and when it attains a sufficient degree of intensity diabetic coma becomes established.

Unfortunately, in the classical type of diabetes there are, as I have previously said, no known means of preventing the disease from advancing from the "alimentary" into the "composite" form; but in many cases, if not exactly in all, the progress may be materially delayed by appropriate dietetic measures of treatment. That this should be the case can hardly be considered surprising, looking at the abnormal state of system that is induced as a result of the transit through the circulation of the sugar derivable from food containing carbohydrate matter.

There is indisputable evidence to show that sugar acts as a toxic agent if allowed to traverse the system. Ill effects of various kinds follow its presence in uncontrolled cases of diabetes, which disappear when the system is brought, by dietetic means, to a natural state as attested by the urine becoming free from sugar. Just as in other directions ill effects are produced by the abnormal presence of sugar in the system, so it can be said to tend to promote the progression of the disease from the mild or "alimentary" into the grave or "composite" form. Experience clearly shows that it tends to act in this way, and support is given to this conclusion by the fact that cases occur in which reversion to the "alimentary" form is susceptible of being brought about by re-establishing a sugar-free state of the urine.

I have been dealing with the subject from the side of progress of the disease in an unfavourable direction. Let me now view it from the opposite side and show what can be effected in the direction of restoration of the power which is at fault, and, thereby, the re-establishment of health.

In a large number of cases it is possible to bring back more or less carbohydrate assimilative power, and even in some to

restore it to an extent to permit of the ordinary dietetic regimen being resumed without being attended with the passage of sugar.

I will take for illustration a case drawn, say, from above the middle period of life, not of very long duration, and yet with the urgent symptoms of the disease having become established. The patient, we will assume, has not been subjected to dietetic treatment, or, if so, not to one of a right nature. As a result, much loss of weight may be taken to have occurred, which simply stands in accord with what might be expected from the escape of the large quantity of food that has been passing off as waste material with the urine. With the loss of weight there will have been loss of strength, both muscular and mental. An inordinate quantity of urine, loaded with sugar, will constitute another of the conditions met with, and thirst will have been proportionate, for it is the outflow of urine occasioned by the egress of sugar that creates the necessity for the extra intake of fluid.

Let such a patient be placed upon a proper diabetic dietary (I shall have something to say hereafter upon what is meant by a proper diabetic dietary), and an immediate beneficial alteration will be produced. Within a couple or three days the urine will be found to have undergone a great reduction in quantity, the thirst will have vanished, and the patient will be able to say that he feels, to a decided extent, more bodily at ease. With these altered symptoms there will be a marked change with respect to the elimination of sugar. It has been within my experience to observe, where the disease has only been of quite recent onset, that within 24 to 48 hours the sugar has disappeared notwithstanding as much as 60 or 70 per 1000, or even more, may have been present at the beginning. Always, there is at once a more or less extensive fall, and the fall may afterwards gradually proceed until the point of disappearance is reached. Here, much depends upon the extent to which the disease has become established. Unless the case is one in which an advanced stage has been reached, the sugar ought to be susceptible of removal from the urine.

Can there be any wonder that the improvement depicted should occur as the result of the changed state induced by the alteration of the food? It does not seem to be realised in the manner it ought to be that the sugar traversing the system is acting in the pernicious way it does. An abnormal state such as that resulting from the filtration of sugar through the system from the food to the urine—for this is the condition that is virtually existing—cannot do otherwise than inflict harm. And, forsooth, in spite of the system being damagingly choked up and oppressed with sugar to the extent it is, it is sometimes said that the carbohydrate of the food must not be cut down because sugar is needed by the tissues. There can be no possible circumstances to render it necessary that the redundancy of sugar existing in the system in the diabetic state should be maintained.

The effect of the altered diet in an acute case of recent onset seems almost like the working of a miracle. Simply by bringing down the sugar, which is at the root of the various troubles belonging to the disease, their subsidence ensues, and brings about a speedy conversion of a sorely stricken state into one of ease and cheerfulness. Even in the course of a few days the change may be such as to give the aspect of a resuscitation to the event.

The maintenance of the improved state has now to be worked for, and subsequently it may prove that something more than a mere check to the elimination of sugar by restriction from carbohydrate food is attainable.

What is really wanted is a restoration of assimilative power over carbohydrate. As long as this is not effected cure cannot be claimed to have occurred. The disease is simply being kept in concealment by not calling for the exercise of a power which does not exist. Tax the power by the administration of carbohydrate food, and immediately evidence will be forthcoming of the defect existing.

It happens, however, that in many cases more or less assimilative power is susceptible of being restored. Indeed, in a case of a promising nature I look for this result to occur. It cannot be foretold when it will happen. Possibly

it may do so at the end of some weeks, but the time is more likely to fall into months instead of weeks. A year or two, even, may lapse without any sign of restoration presenting itself, and then some restoration may occur.

The steady maintenance of the urine in a sugar-free state is a necessary condition for promoting the return of the absent assimilative power. This implies that a natural state of system requires to be brought to bear for giving effect to the attainment of the object in view. Without this help my experience leads me to say that it will be fruitless to look for any satisfactory result being obtained.

I have spoken of the fall in the elimination of sugar that takes place when the treatment of a case with a *properly* restricted diet is first taken in hand; and now let it be supposed that the fall has extended into a disappearance. A disappearance having occurred, there is no reason, in the absence of a dietetic deviation or the supervention of some specially exceptional circumstance, that a return of sugar should set in. With the altered state the health is recovered, the weight that had previously been lost is regained, and altogether the patient may be able to say that he feels as well and as equal for work as ever he had done before.

Whilst things continue in this way, and especially if there should be a continuance of the rise in weight, it may be concluded that no return of assimilative power has yet begun to take place. If, on the other hand, a fall in weight should set in, without any collateral cause to account for it, and particularly if there should be an associated general feeling of malaise, or, as it is sometimes described, a sinking, exhausted feeling, it may be with safety taken, always assuming that the urine has been steadily maintained in a sugar-free state, that some restoration of assimilative power has occurred.

The way to meet the new condition is to give a sparing allowance of starchy food. If a cautious procedure were not adopted, and carbohydrate were given indiscriminately, there would be sure to be an immediate return of sugar in the urine.

I am in the habit of beginning with 3 oz. (85 grammes) of ordinary wheaten bread *per diem* in 1-oz. (28 grammes) portions at each of the three principal meals. If sugar should reappear in the urine, the patient must revert to his former food, but otherwise, as may almost be reckoned to be the case when pronounced indications have existed, the bread may be continued, and subsequently the quantity increased in very gradual stages.

With the allowance of carbohydrate in the circumstances specified the weight rises, and the feelings described disappear, to set in again later if it should happen that the restoration of assimilative power is in advance of the amount of carbohydrate given. In a few exceptional cases I have found that an advance, step by step, has been capable of being made till an ordinary diet has been reached. Usually the advance can be made up to a certain point, and at this point the restoration of power remains stationary, unless something should subsequently ensue to reduce, or, it might possibly happen, but this is less likely, to increase it.

A patient in the condition that has been described is in an analogous position to that of a healthy person, with the exception of the possession of a lower level of carbohydrate assimilative power. As long as the amount of carbohydrate taken is within the capacity existing to dispose of it the urine remains unaffected, but should the amount by ever so little exceed the capacity, sugar will appear in the urine in proportion to the extent to which the capacity has been exceeded. The case can be intelligibly set forth in a very simple way. The carbohydrate which is assimilated is placed in a position to pass to utilisation in the economy, and thence does not find its way into the urine, whilst that which is not assimilated reaches the circulation as free sugar, and flows off in this form as waste material with the urine.

The return of aptitude for taking carbohydrate, without its filtering through the system into the urine as sugar, may be construed as affording evidence of restoration of assimilative power, and, obviously, the amount that can be taken without its doing so gives a measure of the extent of restora-

tion that has occurred. The fact of carbohydrate at one time simply passing through the system and escaping as sugar, and subsequently ceasing to do so, indubitably shows that a restoration of assimilative power over carbohydrate has taken place.

What I have said about body weight and general bodily feeling, especially the former, in relation to returning assimilative power affords a valuable guide in determining when the time has arrived for making trial of carbohydrate food. It is now some years that the facts related have been known to me, and I am constantly putting the knowledge into force as a working basis in practice. The circumstance supplies a felicitous illustration of the adaptiveness met with in nature. Where no assimilative power over carbohydrate exists carbohydrate cannot be wanted by the system. In fact, if given, it simply filters through the system into the urine, and in its passage inflicts harm. As soon, however, as assimilative power becomes restored, the carbohydrate that can be assimilated is wanted, and evidence of such being the case is afforded by the loss of weight that sets in if the appropriate amount is not given.

It is well known that in a state of health reduction of the supply of carbohydrate has the effect of lowering the weight. The fact is turned to account in the treatment of obesity. With each step of advance in the restoration of carbohydrate assimilative power there is a step of approach towards the natural state. What is therefore observed in connection with the fall in weight with returning assimilative power, where the circumstances are not met by an appropriate supply of carbohydrate, is only in harmony with the principle that dominates the result under healthy conditions.

Should it happen, as is within the range of possibility, that, through error of diagnosis, a patient is placed upon a diabetic diet where diabetes in reality has not existed, the result to be naturally looked for is a decrease in weight. I have seen cases of the kind, and the fact of decrease having followed the alteration in diet has helped to establish the point that actual diabetes has not existed. True diabetes is,

through the circumstances belonging to it, attended with loss of weight, and when the diet is altered the weight goes up.

Thus the effect of carbohydrate food is diametrically opposite in diabetes and health. Where carbohydrate assimilative power does not exist the effect of giving carbohydrate is to lower the weight. Not being assimilated, it simply passes off as waste material, and, by its baneful influence in its transit through the system as sugar, interferes with the proper performance of the nutritive and other processes of life. Persons sometimes think that carbohydrate should be given to check loss of weight. This idea is rightly applicable where the power exists to turn it to account, but if the power should not, as in diabetes, exist, the supply of carbohydrate cannot be otherwise than, in the first place, useless, and, in the next, positively hurtful by adding to the abnormal state existing.

What is wanted is that the circumstances, as they present themselves, should be rationally dealt with. If carbohydrate throws sugar into the urine it is unreasonable to give it, and with the body weight maintained upon the diabetic diet, as it is where assimilative power has not been restored, proof is afforded that the diet is adequately meeting the requirements of the system. When carbohydrate is found to be tolerated, the quantity allowed should be adjusted to the assimilative power existing, avoiding, however, running too close to the border line of toleration.

The principle of action to adopt is to give as much starchy food as is found to be consistent with the maintenance of a sugar-free state of the urine, and to carry out this the urine requires to be vigilantly watched. I am in the habit of asking for a specimen of the urine passed on going to bed at night, and another of that passed on rising in the morning to be brought for analysis. The one is under the influence of the food taken during the day, and the other under that of absence of food during the night, and it is ordinarily found that a difference is noticeable between the two—that the one under the influence of food may contain a certain amount of sugar, whilst that after the night's fasting contains none.

Because assimilative power may be regained so as to permit

of a more or less complete return to ordinary food it does not follow that things will always remain in this position, and, especially so, if indiscreet indulgences are allowed to occur. Persons are apt, when they get back to ordinary food, to think that they are exempt from liability to a return of the sugar. This is not the case, and unless caution is exercised a relapse that may grow into one of a severe nature may, even after a period of some years, set in, requiring for relief, if such is again obtainable, a return to the treatment that was before adopted.

The sugar traversing the system constitutes, certainly in the alimentary form of diabetes, the cardinal deleterious factor of the disease. It is true, the loss of food material through its escape as sugar with the urine, and the irritating topical action of the sugar-containing urine that is sometimes observed to occur, of course constitute hurtful results arising from the disease, but, with the exception of these, the results met with constitute effects of the baneful influence of the sugar abnormally present in the blood. There must necessarily be a foundation for the abnormal presence of sugar in the blood, but this has nothing to do in a direct manner with the production of the symptoms of the disease. Food, in the alimentary form of diabetes, is the prime moving source of the sugar. Remove by dietetic measures the abnormality as regards the sugar and a disappearance of the symptoms will occur, but will be followed by a return of them if the absence of the abnormality is not maintained. This proves that the sugar is the agency that occasions the mischief.

Virtually it is the toxic action of the sugar present in the blood that gives rise to the ill effects upon the system produced by diabetes. Various kinds of structural damage are known to be inflicted, and they stand in keeping with those produced by alcohol and other toxic agents. Indeed, as regards the kidney and the nerves, the closest analogy is to be traced between the effects of alcohol and of sugar. In diabetes, sugar is holding a wrong position in the body, and in this wrong position it constitutes a true toxic agent—a fact that is not generally realised in the manner it should be.

The point to be now dealt with is: From what source does the sugar abnormality arise? Primarily the sugar comes from the food. This is beyond question shown by the fact that carbohydrate food gives rise to the abnormality, and that under withdrawal of the carbohydrate food the abnormality disappears. Traced to the food, the next point is: Does the condition come from erroneous entry of sugar from the food into the circulation, or does it come from non-removal in the systemic capillaries by failing to become disposed of as it should be? This brings us to the fundamental propositions: Is it right that there should be an entry of free sugar into the circulatory system from the food for functional transport to the tissues for utilisation? and: Is it possible for such to occur without being attended with a corresponding flow of sugar into the urine?

Let attention be given to the matter from the point of view of failure of proper metabolising action in the tissues. Let it be supposed that sugar fails to be used up by the tissues as it ought to be, and that through this a backward effect is produced which might account for the abnormal presence of sugar in the blood. If it were presumable for such to exist, it must be said that there is no evidence to give support to it. Not the slightest indication is presented of faulty tissue metabolism in the class of case that is under consideration during the maintenance of a sugar-free state of the urine. The person appears in a perfect state of health and is full of vigour and activity. The only distinguishing feature between such a person and a person in a normal state is in the effect upon him of carbohydrate food. Give him carbohydrate food, and it will be found that he cannot tolerate it without passing sugar in the same manner as the healthy person can.

Muscle and nerve functionate just as in healthy people, and for this to be the case there cannot be any failure of oxidising action in the tissues. Surely if the fault were situated here there ought to be some indication of defective tissue action. Further, by what mechanism could the transit of sugar to the tissues be regulated so as to secure, under the varied conditions of life, that at all times the whole is abstracted and

disposed of? Should this at any time not happen to be the case accumulation must occur and affect the urine.

In diabetes, where sugar derived from the food is in reality permitted to reach the tissues through the circulation, the slightest dietetic alteration is found to tell immediately upon the urine. Let a case be selected in which carbohydrate can be taken up to a given limit without affecting the urine. In such a case, no matter what the circumstances of life at the time, as long as the quantity taken remains within the fixed limit of toleration the urine shows no signs of being affected; but should the quantity, by ever so little, exceed the limit, sugar will immediately appear in the urine in proportion to the extent to which the limit has been exceeded. To account for this occurrence under the supposition that it is right for sugar from the food to be carried to the tissues to be there taken and disposed of, it would have to be assumed that, in spite of the varied conditions of life, the quantity of sugar that can be taken and disposed of by the tissues persistently stands at an unvarying point, a position that can hardly be looked upon as tenable. Under the assimilation view, on the other hand, that has been propounded, it is quite intelligible that the assimilative power existing in different cases should have a definite boundary line, which is the factor in determining whether sugar reaches the general circulation or not. Indeed, in healthy persons this boundary line exists, and when the carbohydrate ingested stands above the amount that can be assimilated, sugar reaches the circulation and thence the urine.

It is stated that in the diabetic the respiratory quotient is below that of an ordinarily fed man. Now, if carbohydrate is not properly assimilated on absorption, and thence is permitted to reach the general circulation as sugar which flows off with the urine, there is nothing in the position of things but what might be naturally looked for, seeing that the carbohydrate fails to properly reach the tissue elements. If there are circumstances to lead to carbohydrate simply passing through the system without being retained in it, the position is the same, as far as the tissues are concerned, as though there was no supply of carbohydrate at all.

The doctrine of glycolysis, which has been advanced to account for the destruction of the sugar assumed to be reaching the circulation, I consider cannot be regarded as having any substantial foundation, and this view, I think, is for the most part entertained by others.

Nothing but mysticism and incompatibility confront us if we view diabetes from the standpoint that has hitherto been taken—viz. that there is a functional transit of sugar through the circulation, and that the disease arises either from an excessive influx of sugar or a deficient efflux for appropriation by the tissues. Viewed in the manner I have contended for, everything consistently fits in and stands intelligibly before us. In representing what occurs, no complicated disquisition is needed. A few plain and precise words suffice for placing before the mind the position in which things stand; and under the view adopted a light is thrown upon diabetes which renders it one of the simplest of conditions to understand. At the same time, it may also be said that through the doctrine propounded the foundation is laid for the treatment of the disease upon rational lines of procedure.

We have these facts before us: Under normal conditions the carbohydrate ingested is subsequently neither discoverable in the blood nor in the urine; in diabetes it is discoverable in both, and the sugar eliminated with the urine stands in accord with the carbohydrate ingested. In the one case, the carbohydrate disappears from view and evidently passes to utilisation; in the other, it filters through the system into the urine in the form of sugar and thus becomes discharged in an unutilised condition. To what is this difference attributable? I say it is due to the carbohydrate being assimilated—that is, synthesised into proteid (there is evidence to show that a large amount of carbohydrate can emanate from proteid) and transformed into fat—at the seat of absorption, and supplementarily converted into glycogen and fat in the liver, in the one case and not in the other. If assimilated, it is prevented reaching the circulation as free sugar, and consequently does not reach the urine. If not assimilated, it

reaches the circulation as sugar and thence flows off in conjunction with the urinary water.

The issue then depends simply upon whether the carbohydrate is assimilated or not, and it will be noted that the assimilation must occur before the general circulation is reached. Assimilation in the capillaries of the tissues would mean transport of sugar through the circulation to them, and this would further mean that in proportion as such occurred so would the urine be charged with sugar.

Carbohydrate assimilative power is thus brought into the position of ruling factor in connection with diabetes. When the carbohydrate to be assimilated is within the power existing to assimilate it the urine escapes being influenced. When, on the other hand, the carbohydrate is in excess of the power to assimilate it so, in proportion as it is so, will sugar make its appearance in the urine. In a state of health, it has to be said, the power does not exist to an unlimited extent. With every one the urine may be rendered saccharine by giving carbohydrate, particularly in the form of sugar, in sufficiently large amount; and probably amongst healthy persons there are varying degrees of power to be met with, giving rise to a less aptitude for taking carbohydrate without passing sugar in the case of one person than in that of another.

From the range of power that may be considered as representing the healthy standard examples present themselves of successive steps of diminution until the point of extinction is reached. The mild forms of reduction of power give the cases which are ordinarily classified as cases of glycosuria, and in some of these the diminution from the normal standard may be so slight that it is only when an extensive amount of carbohydrate has been taken that sugar is found in the urine. Such cases not infrequently give rise to much perplexity on account of the variable state of the urine, but there is nothing inexplicable about them when viewed from the standpoint I have suggested. When the reduction of power is great, it is only with full exclusion of carbohydrate food that the urine can be rendered free from sugar. These cases typify a

more advanced faulty condition and authentically fall in the diabetic category.

For the varying amounts of assimilative power existing in different cases, the sharpness of the boundary line is something quite surprising. Up to a definite point, but no farther, the carbohydrate can be given without leading to the appearance of sugar in the urine. The slightest excess tells immediately—that is, within the next two or three hours—upon the urine, and afterwards the effect is no longer observable, unless renewed by a fresh excess. An apple, a glass of milk, or a slightly extra quantity of starchy food, is quite sufficient to produce an output of sugar with the urine. Dietetic deviations thus become easily susceptible of recognition.

I have before spoken of the attention that is necessary to be given to the urine in order to guide the management of a case. I have also referred to the fact that after the food of the day sugar may be found, whilst after the night's fasting there may be none. The period of the twenty-four hours most likely to show the influence of food is that comprising the first few hours after breakfast. This I confidently affirm, and the explanation may possibly be that absorption is then more actively carried on than at any other time, and through this there may be escape from assimilation, which with slower absorption would not occur.

Following as it does from what has preceded, that the essential point to be dealt with in the class of case that has been considered is defective carbohydrate assimilative power, the object to be attained is clearly a restoration of the missing power. Restore the power and diabetes would no longer exist, for then carbohydrate could be taken, and the power of assimilating it having been regained, there would be no sugar in the urine.

Now, many cases permit of this aim being carried out; some of them, it may be said, especially if the condition is taken early, completely, and others to a greater or less extent. One great aid towards attaining what is wanted, even if it is not the main point in connection with the matter, is bringing the system to a natural state by checking the passage of sugar

through it. As long as the abnormal condition arising from the transit of sugar through the circulation from the food to the urine is allowed to exist it is futile to expect that any improvement can take place. Indeed, experience shows that progress in the reverse direction ensues, and that the disease assumes a more and more established and aggravated form. Wrong structural and functional states become developed purely as effects of the toxic action of the sugar, and these in their turn exert an intensifying influence upon the faulty condition which is at the foundation of the disease.

As previously stated, we only know of diabetes through the effects produced by the sugar present in the system. Necessarily there must be a primary condition to lead to the abnormal presence of the sugar, but this does not in any way reveal itself except through the effects of the sugar, the abnormal presence of which in the system it determines. Remove, through the instrumentality of appropriate dieting, the sugar item of consideration from the case, and there is no longer the slightest indication to be perceived of the existence of diabetes. The primary abnormal condition, however, which stands at the foundation of the disease is still there, as may at any moment be rendered evident by giving carbohydrate food.

To the sugar, undoubtedly, must be attributed the various troubles met with in connection with diabetes. I do not think this is sufficiently realised, or greater and wider significance would be attached to getting the sugar as thoroughly under control as it is possible to do. That the sugar in the system is, in reality, the prime factor at the root of the troubles is shown by the dependent relation they hold to it. As long as the sugar can be controlled the patient can be kept in a perfectly good state.

In the classical type of case it is the progressiveness of the fundamental condition which gives the formidable character to the outlook. In the first stage there is only the effect of faulty assimilation, which can be controlled by not giving the food that fails to be assimilated. Subsequently there is a faulty tissue breaking down, attended with the liberation of

sugar, and now the elimination of sugar is no longer susceptible of control. As a result of the extended faulty metabolism that has set in, certain acid products make their appearance in addition to the sugar, and it is these which give the gravity to the stage of the disease that has now been reached. Their effect is, by virtue of their acid property, to tell upon the constitution of the blood in a manner to affect its carbonic acid transport capacity, and through this to lead to the production of coma. Arising as these products do, in the class of case under consideration, from an uncontrollably advancing condition, it is only a question of time before the degree of acidosis attains sufficient proportions to bring about a fatal issue.

When the production of these acids sets in, we have a second toxic agency to deal with, but previously, as I have said, all the tangible conditions appertaining to diabetes arise from the sugar abnormally present in the blood. The sugar constitutes as much a direct toxic agent in the system as alcohol, lead, arsenic, mercury, etc. A great variety of morbid effects, wrought upon different parts of the system, are produced by it, in like manner as occurs with alcohol, and in all instances the only means of effecting their removal is by working through their prime cause and by getting rid of it from the system. When relief is obtained, the sugar must continue to be kept under in order to prevent a relapse occurring. I have dealt with these matters in an article, "On Diabetic Neuritis," published in the second volume of the *Lancet* for 1904, pp. 17 and 71, and in another, "On Albuminuria as an Accompaniment of Diabetes Mellitus," in the second volume of the *Lancet* for 1903, pp. 1495 and 1572. To these I may refer for detailed particulars.

Amongst the ill effects produced by the sugar abnormally present in the system is the promotion of the passage of the disease from the "alimentary" into the "composite" form. To this subject I have already incidentally alluded, but it is one which deserves a fuller consideration. With the passage into the "composite" form there sets in a wrong tissue breaking-down process, attended with the liberation of

sugar. Instead of katabolism proceeding by successive steps until carbonic acid and ammonia (urea) and water are produced, with full disengagement of the energy locked up in the original molecule, it halts, in a halfway sort of manner, with the setting free of principles still containing unutilised energy. Sugar and the acetone series of products (β-oxybutyric acid, diacetic acid, and acetone) become thus disengaged, and find their way into the urine. It is easy to realise that when this faulty katabolism exists in addition to the faulty anabolism or assimilation of carbohydrate a serious aggravation of matters is induced.

The acetone series of products particularly constitute a source of injury; for, not only do they create waste, by carrying off unspent energy, and conduce to structural damage within the body, but, in a side way, they imperil life by interfering with one of the most important functions of the economy. It is as necessary for us that the carbonic acid produced as a result of the operations of life should be conveyed from the tissues to the lungs for discharge, as that oxygen should be conveyed from the lungs to the tissues for utilisation purposes. Now, the conveyance of the carbonic acid is effected mainly by the agency of the carbonate and phosphate of soda in the blood. These take up the carbonic acid developed in the tissues and transport it to the lungs, where it becomes liberated and discharged.

Such is the physiological explanation given of the manner in which carbonic acid finds its way out of the system. In "composite" diabetes the acids, generated as a result of the faulty katabolism occurring, appropriate the sodic alkali, and, forming a compound which cannot take up carbonic acid, deprive this body of its proper means of escape from the system. The condition may be experimentally brought about by the introduction of an acid into the blood, and "acidosis" is the term that has been applied to it. It constitutes the source of diabetic coma, and therefore has bearings of serious import.

The production of the abnormal condition that has been referred to is not confined to association with diabetes. It

is noticed to occur as a result of starvation and sometimes in connection with febrile diseases, especially in children. Other conditions have been mentioned with which it has been found to be associated. Amongst these is the exclusion of carbohydrate food in the non-diabetic by restriction to a flesh and fat diet.

In the typical form of severe diabetes the "acidosis" state becomes developed as an intrinsic part of the disease during the progressive course taken by it. In children this occurs early, and afterwards continues steadily on, notwithstanding the sugar for awhile may have been removed.

Considerable diversity is observed with regard to the supervention or not of "acidosis." It is through diacetic acid, by means of the ferric chloride reaction, that the condition is ordinarily looked for and gauged, so that "diaciturial" in reality is ordinarily taken as representative of the "acidosis."

Cases of the class to which I am now referring may run on for a great number of years without showing any disposition to pass to the stage of "acidosis" complication, although the urine may not even have been maintained in a sugar-free state. It is usual, however, when the urine is not kept free from sugar, to find that the case runs on with a higher or lower rate of advance to the stage in question. In adults there is less proneness for "acidosis" to set in than is noticeable in children, and in the former, as long as the urine can be kept free from sugar, the patient seems to be safe against the supervention of the complication. I am not aware that it has fallen within my experience to see "acidosis" become developed whilst the urine was being maintained in a sugar-free state.

Where the case is one of an intrinsically progressive nature, and where the sugar has been, in the first instance, removed, the first unfavourable event is a reappearance of sugar upon the diet which was previously successful in keeping it absent. Afterwards "acidosis" sets in and stamps the passage of the malady into a stage of greater gravity. But even now it does not necessarily follow that a rapid termina-

tion is imminent. It is possible for the rate of progress, especially in somewhat advanced life, to be slow, and for the acetone group to be present to a moderate extent in the urine of patients for, I can say from experience, certainly some few years.

I will now give attention to the reciprocal relationship existing between the condition attended with sugar in the urine and the acetone group of products, in order to ascertain what guidance is afforded by it. The matter is one of much importance, as upon it rests the view of what constitutes the right line of action to be taken in connection with dietetic management.

On the one side, the fact is before us that the abnormal state of system produced by the sugar derived from defective dieting in diabetes encourages the development of the wrong katabolism which gives rise to the acid products. It is only reasonable to expect that this should be the case, seeing that the condition of the patient being in every respect made worse, the progress of the disease into its worst form is hastened on. That what I have stated is true is proved by the fact that the diaceturia which has shown itself where the disease has been allowed to run on uncontrolled by proper dieting is usually found to be susceptible of being made to disappear, by bringing the urine to a sugar-free state through the adoption of the requisite dietetic measures for the purpose. And there is a further fact that, if in such a case conditions are allowed to fall back, by relaxing the diet, into their former position, a return of the diaceturia may be confidently looked for, susceptible, perhaps, of being removed a second time by a return to the measures which proved successful before.

On the other side, exclusion of carbohydrate from the diet causes, not invariably, but frequently, an appearance of diaceturia in cases where it did not previously exist. This is a comparable kind of effect to what has been observed in the non-diabetic as a result of starvation and of restriction to flesh and fat food. When diaceturia already exists, it becomes to a certain extent augmented. The effect may

only be of quite a mild and temporary nature, and, certainly, where diaceturia has not been previously existing, it may be trustingly expected to subside and disappear in the course of a short time. Where diaceturia has previously existed, the issue from the altered dieting will depend upon the stage to which the disease has advanced. If not too far advanced, as time progresses the diaceturia may be looked for to diminish and, ultimately, to disappear, but some weeks, or even months, may elapse before this final result is attained.

I may refer to articles in the first volume of the *Lancet* for 1900 and the second volume for 1902, in which I have dealt with these matters and given illustrative cases, under the respective titles of "Differentiation in Diabetes" and "On the Acetone Series of Products in connection with Diabetic Coma."

In the circumstances that have been detailed, it may be asked: How are we to act in dealing with the class of case above referred to? The chance of inducing diabetic coma by "acidosis" augmentation has been advanced as a point against putting into force the diabetic dietary. I have further seen it suggested that the "acidosis" question should engross attention in preference to that of the sugar. Superficially this might appear to be entitled to consideration, but the matter requires to be more deeply looked at to permit of a proper judgment being formed.

In the "alimentary" case, which is the type to which I am referring, the "acidosis" is secondary to the sugar. It would not be present if the urine had been maintained in a sugar-free state. The toxic action of the sugar traversing the system from the food, amongst the deleterious effects produced, promotes, as I have before mentioned, the wrong katabolism that gives rise to the formation of the acids concerned in the matter. If carbohydrate food is not withdrawn, the promoting cause of the "acidosis" will continue in operation, and lead to things becoming worse and worse. Observation unequivocally shows this to be the result that occurs. The only way of reducing and removing the

acid principles is by reducing and removing the toxic agent (sugar) which is contributing to their production ; and, if this is done, observation further shows that their removal is in the course of time susceptible of being effected, unless it should happen that the case has reached too advanced a stage. Hence, instead of being scared from withdrawing carbohydrate food under the circumstances that have been referred to, there is nothing else to be done to afford the opportunity for improvement.

Judging from my own experience, the risk of serious consequences accruing from the withdrawal of carbohydrate food is much overrated. Often, as I have before stated, no diaceturia is produced by suddenly putting into force the diabetic diet. At other times, a certain amount of diaceturia follows, but soon disappears. I am in the habit in every case of having the urine examined for diacetic acid and acetone as well as for sugar, and follow the custom that has been introduced of having the two former quantitatively represented by symbols. Their absence is represented by O and their presence by +, numerically repeated to the extent of four or it may even be to five, according to the degree of reaction obtained. Where O has represented the condition before the alteration of diet, there may be one or two plus marks, but, as a rule, not more, to be afterwards assigned. If there have been plus marks before, they are about correspondingly increased after. This is the extent of alteration produced by food.

Now, if there is no diaceturia existing when the patient falls under observation for treatment I do not consider there is the slightest risk incurred in passing at once to the fully restricted diet for diabetes. I say this upon the strength of my routine experience, for it is my invariable practice in such cases to do so, and I have never seen any ill effect from it.

In the interest of the future in connection with the management of the case, I consider it very desirable that such a course should be adopted. If the patient is told that it is necessary at once to commence the altered dietary, he realises the principle of action he has to proceed upon, and is

in a frame of mind to be impressed with the importance of implicitly complying with the instructions given. If, on the other hand, he is desired in the first instance to commence with a half-measure treatment, he will not be struck in a similar manner with the importance of the part played by the exclusion of carbohydrate food, and will not understand the force of having to take his second step. Thus only in a half-hearted way will he enter upon the course, which requires strong conviction and determination of will to persevere in carrying out.

A patient understands the meaning of and is ready enough to fall in with the advice to return to some starchy food, when it is permissible for him to do so, but he does not so readily understand the force of being obliged to take a step in the opposite direction. The immense bodily improvement that follows even in a couple or three days the start upon a full change of diet serves in the fullest manner to establish in the patient's mind the benefit derivable from attention to food, and thus affords encouragement for the exercise of steady perseverance in following the course that has been commenced.

Should diaceturia already have set in, the physician must be guided by the extent to which the "acidosis" has advanced. If the diabetes has been in existence for some time, and has reached an advanced stage, with strongly-marked "acidosis" present, it is only natural to consider that danger would attend any abrupt alteration of the internal state of the system, no matter in whatever way induced. It is well known that persons in an advanced stage of the disease hold a precarious tenure of life, and that a very little disturbance of any kind suffices to throw them into a state of diabetic coma. Over-fatigue, an attack of vomiting, obstinate constipation, the supervention of influenza or pneumonia, and various other conditions, may suddenly lead to the occurrence of coma—in other words, induce an increase of the "acidosis" to an extent to prove fatal. Such being the case, it would not be wise to subject the patient to the disturbing influence of a sudden transition of any kind, and for this reason an

abrupt change of diet is, under the circumstances depicted, to be avoided.

If diaceturia should not exist to any pronounced extent, and, particularly, if the disease has not been of long duration, and thus has not reached an advanced stage, I consider, upon the strength of experience, that there are no grounds against adopting the ordinary course and placing the patient at once upon the diabetic diet. If thought advisable, the precautionary measure might be taken of giving the sodic carbonate freely, with the view of putting into the system more alkali to meet the abnormal acid production.

Without wishing to say anything to lead to less importance being attached to the "acidosis" question than justly belongs to it, I at the same time feel it right to state that I consider the matter is in some quarters being dealt with in a manner to prove prejudicial to the interests of patients. If used as an argument against the dietetic exclusion of carbohydrate in diabetes, I emphatically assert that much harm cannot fail to be produced. The only means at our command for prolonging life and maintaining a satisfactory bodily condition are those which are capable of bringing a controlling influence to bear upon the sugar which is acting perniciously within the system. If ideas upon the "acidosis" topic should frustrate the judicious carrying out of this object, I unhesitatingly aver that it will be at the cost of health and life to those suffering from diabetes.

The question now confronts us, What does a proper dietetic treatment of diabetes mean? Seeing that the abnormal presence of sugar in the system is the source of the various troubles met with in connection with the disease, and that carbohydrate food is the source of the sugar, the rational course of procedure that suggests itself to be pursued is to eliminate carbohydrate from the diet.

Observation shows that it is especially in food from the vegetable kingdom that carbohydrate is present. It is not correct to say that animal food is free from carbohydrate, but the quantity it contains is sufficiently insignificant to prevent any difficulty being experienced in drawing suitable food

from the animal kingdom. There is no doubt that a mixed diet is the one for which we are constructed by Nature to subsist on, but our power of adaptibility to varied conditions is such that we can thrive on food drawn exclusively from either the animal or the vegetable kingdom.

The difficulty, then, specially lies with food from the vegetable kingdom as regards accessibility to articles sufficiently free from carbohydrate to be suitable for employment; and if it were not for the fact that carbohydrate in the form of cellulose is, through its resistance to attack by the digestive juices of the human subject, permissible to be taken, the difficulty would be much greater than it is. Starch and sugar, unfortunately for the diabetic, exist in large quantity in a great number of products derived from the vegetable kingdom, and as these principles require to be excluded from his diet, his dietary has to be framed upon the dictates of a knowledge of the chemical composition of the individual products. It is only upon this basis that it is permissible to take action.

Starch and fat represent the non-nitrogenous constituents of a large number of seeds. They hold a sort of complementary relation to each other, sometimes the one and sometimes the other being mainly present, and sometimes a considerable quantity of each. What are known as the "oily" seeds constitute suitable food for the diabetic; and, as far as diabetes is concerned, it is unfortunate that the farinaceous instead of the oily seeds were selected by our ancestors as the basis of staple food from the vegetable kingdom. It may be considered that it was purely a conventional procedure to make the selection that was hit upon, and chemistry tells us that in the oily seeds, like the almond, etc., the food principles are more proportionately in conformity with what they should be to meet our requirements than in those of the cereals.

The great *desideratum* in the diabetic dietary is an article to take the place of our ordinary wheaten flour bread. To Bouchardat the credit is due of having been the first to make attempts to supply a diabetic bread. At his instigation the starch was removed from wheaten flour by washing, and the

separated gluten made into bread. To this day the procedure has continued to be adopted, and gluten bread still holds its ground as an article of food for the diabetic.

The chief point of objection connected with gluten is that it is found to constitute a very variable article in relation to its suitability for use as diabetic food. According to the extent of removal of starch so will be its fitness for use, and it depends on the probity of the manufacturer whether much or little starch is removed. Unfortunately, in connection with this point, it happens that the market value of starch is signally less than that of gluten. Unfortunately, also, upon other grounds, the incentive is not supplied to render purity from starch the sole object of consideration. It infelicitously happens that the less the purity of the gluten, the more palatable the food that can be made from it. This is realisable from the fact that the larger the amount of starch present, the nearer will the manufactured food approach in character that derivable from ordinary wheaten flour.

Despite the importance of the matter, it is grievous to find that there are gluten preparations to be met with containing so much starch as to be quite unfit for the purpose for which they are sold. For successful treatment it is requisite that the physician should know whether he is on safe ground with respect to the food he recommends to be taken. For my own part, I have felt it necessary, as a professional obligation, to make myself personally acquainted with the composition of the various articles supplied; and from the knowledge thus acquired I have learnt much that has proved of valuable assistance in clearing up apparent anomalies connected with different cases. I need not enter into details of the analytical procedure adopted. It is sufficient to say that the starch has been estimated in the form of glucose, after having been hydrolysed by boiling with dilute hydrochloric acid. Previous to analysis the articles have been brought to a water-free state, and in this way placed in a position to yield results uninfluenced by the chance amount of water present, and thus admitting of comparison with each other.

It has sometimes fallen within my experience to meet with

from 50 or 60 to 70 per cent. of starch in the so-called gluten food; and yet it was being consumed under the supposition that it was the right thing to be taken! Dieting with food of such a nature may be looked upon as constituting a mockery of what diabetic dieting should be. In former years provision was not made for restricting the food supply of the diabetic to articles of the standard of purity that is now considered requisite, and, coincidently with this, treatment was then attended with far less effective results than it is now. My own experience enables me to state that diabetes has been divested, through the greater success attending the treatment of the disease attributable to the improved dietetic resources now at command, of much of the alarm-exciting character that belonged to it in former times.

I have spoken of food that fails to represent what is wanted to meet the requirements of the proper dietetic treatment of diabetes, and which thus cannot do otherwise than prove disappointing to both physician and patient; and now I will refer to food of a right nature. It is satisfactory to be able to state that there are a few high-class establishments at which food that can be relied upon is obtainable. Not only is purity with respect to exclusion of carbohydrate regarded as a first consideration, but, with very commendable zeal, attention has been given to palatableness and to the provision of variety in different directions. Without hesitation it can be said that, with the supply of the specially made food that is now at the disposal of the diabetic, his lot has been rendered infinitely more bearable than it was in former times. It is in the *cuisine* department, and in this only, that the life of the diabetic requires to differ from that of ordinary people, and anything which contributes to making things more easy for him in this direction is deserving of encouragement.

So much improvement has been made with respect to purity of the food supplied that the urine of patients can now be brought into a sugar-free state, and maintained so, to an extent that was not formerly possible. Except in bad cases, I look for this result to be brought about; and then, in many instances, a return of assimilative power follows, permitting

of a certain allowance of starchy food being with advantage taken. This is a matter that I have already dwelt upon, and, when doing so, stated that the amount of carbohydrate matter allowed requires to be adjusted to the assimilative power existing, the principle to be followed being to give as much as can be taken without leading to the appearance of sugar in the urine.

Formerly gluten containing 25 to 30 per cent. of starch was found to represent the extent to which the extraction of starch was carried. Obviously, the less the amount of starch the better is it suited for employment as diabetic food, and it is a step in the right direction to be enabled to say that it is now procurable with a less than 10 percentage of starch. A point that may be regarded as of high import is that the good maker of food appeals to analysis as his basis in selecting the gluten he employs. It is only in this way that he can place himself in possession of a reliable knowledge of the condition of the article.

Gluten, at first, almost exclusively represented the material available for the production of a bread-stuff substitute for the diabetic. Bran was subsequently introduced, but, unless thoroughly washed with boiling water to remove adhering starch, it must not be considered to be suitable for employment. The almond and some other oily seeds have come into somewhat extensive use. The latest to be brought forward is the proteid of milk. This is an invaluable material for the purpose under consideration, and it admits of being prepared upon a sufficiently large scale to adequately meet any demand that may exist. An immense advantage belonging to it is that the nature of its mode of preparation is such as to yield a pure proteid, free from the risk of contamination with carbohydrate.

I come now to speak of certain foods which are largely advertised as food for the diabetic, but which have no claim to be so considered. I refer to wheaten flour preparations in connection with which it is not contended that any extraction of starch has been effected, but is stated that the starch has been altered and put into a form to render it suit-

able as diabetic food. It may be confidently asserted that this does not admit of being done. From established knowledge with regard to starch it can be safely said that no change, short of absolute destruction as organic matter, will prevent its passing in the form of sugar, like the original starch, into the urine of the diabetic. Observation upon diabetic patients testifies to the truth of this statement; and if, in any case, the food in question is found to be tolerated, it is because sufficient assimilative power exists to effectually deal with it, and the same result would be noticeable if a corresponding amount of ordinary bread were taken instead.

In connection with the question of food, I consider it desirable, although the matter in reality is subordinated to the general principles that have been enunciated, to say something about the "potato treatment of diabetes" which has been recently engaging attention in a somewhat conspicuous manner. I am able to recall other treatments in which the administration of carbohydrate has formed the intrinsic factor. I remember treacle having been advocated, and also honey. Sugar also enters into consideration in connection with the "skim milk treatment." With respect to the "potato treatment," a series of articles have been published by A. Mossé, of Toulouse, in the *Revue de Médecine* for 1902, in which it is made to appear that starch as it exists in the potato does not produce the same baneful effect as an equivalent amount taken in the form of bread. This is all that is contended for, and the difference is accounted for in the following way (pp. 623, 624): In the first place, by the water contained in the potato, about six times greater than that contained in an equivalent ration of bread, the thirst and the sensation of dryness of the mouth are diminished; and in the next, by the potash which is present in notable proportion, combined with organic acids, the alkalinity of the system is increased and glycolysis thereby favoured. Further on he says that the employment of the potato may be likened to an alkaline treatment, with the particularisation that potash is substituted for soda.

My experience stands diametrically opposed to the proposi-

tion that has been alluded to, and I consider, if it had not engaged attention to the extent it has done, that it would not be worth discussing. The virtue of the treatment is stated to depend upon water and alkali. These are most accessible agents, and yet it has not been learnt that, apart from the aid of restricting the supply of carbohydrate, they are capable of producing any absolutely demonstrable effect. I distinctly aver that there is nothing for a moment to warrant the belief that the substitution of potato starch for wheaten starch could make any difference.

The potato treatment of diabetes has not been without an eager advocate in this country. In a recently published work[1] it has been extolled in laudatory terms, and the permission of potatoes to diabetics has been spoken of as "one of the greatest of the dietetic advances of our times"(!). Unfortunately, precept and practice are not always in accord, and in my contact with medical practitioners it has fallen in my way to hear words bearing a stamp of resentment expressed at the manner in which, notwithstanding the "steaming of the tuber in its jacket" as enjoined was carried out, the expectations that had been raised failed to be realised.

Seriously considered, it may be said the potato is perfectly allowable where sufficient assimilative power exists to permit of its being taken without throwing sugar into the urine. In these circumstances, it does not signify from what source the diabetic draws his starchy food, but the adjustment must be made with regard to quantity so as to secure that the boundary-line of power is not overstepped and sugar made to appear in the urine.

I have seen the argument adduced that potato, with its about 20 per cent. of starch, ought to be considered as suitable for the diabetic as a substitute for bread containing a corresponding proportion of starch. No comparison, however, can be permissibly drawn between an article consisting of three fourths water and another in a practically dry state. Moreover, what ought to be looked upon as a proper representative in the diabetic dietary of bread-stuff food should be in a

[1] *Contributions to Practical Medicine*, by James Sawyer, 1904.

better state with respect to percentage of starch than that given by the above figures for potato.

It may be asked: What is the use of a diabetic dietary if it does not bring the system into a more natural state by reducing the amount of sugar abnormally passing through it? Mossé says glycosuria is not the disease. In this he is perfectly right, but the glycosuria is attributable to the sugar abnormally present in the system and is an indicator of its amount. If there is any glycosuria, it means that there is more sugar in the system than can be properly dealt with by it. It can be positively affirmed that the only way open for reducing the sugar is by reducing the carbohydrate ingested. The glycogenic doctrine leads up to the idea of a flow of free sugar from the food and the liver through the circulation to the tissues, where it is spoken of as being burnt. The entire experimental ground upon which this view was based may be taken to have disappeared, and I appeal to what has been stated in the early part of this work for demonstrative evidence of such being the case.

Authorities everywhere admit that dieting so as to restrict carbohydrate constitutes a necessary part of the treatment of diabetes; but looking at the manner in which it is in many quarters carried out, it resolves itself more into a nominal than a real application of the principle. At the present moment on the Continent there seems to be an idea afloat antagonistic to the full exclusion of carbohydrate food. Mossé, to quote from him again, says: "Carbohydrate is indispensable to the diabetic."[1] If by carbohydrate is meant carbohydrate food, I absolutely deny the truth of this statement. The glycogenic doctrine apparently is at the foundation of the idea, it being assumed under it (contrary, as I have just stated, to the evidence now before us upon the matter) that a transport of sugar normally takes place through the circulatory system from the food to the tissues. Viewing things in that way, it has been thought that carbohydrate should not be cut off, notwithstanding we are in reality faced with the fact that the system of the diabetic

[1] *Revue de Médicine*, 1902, p. 108.

is suffering from the effects of over-repletion with sugar. Could there be anything more in conflict with reason? The tissues are bathed with blood, admittedly, on all sides, containing a superabundance of sugar, and yet carbohydrate is to be supplied, the effect of which is to add to the already existing superabundance. We have only to look to the carnivora for the supply of evidence that carbohydrate food is not indispensable for the maintenance of animal life. It is true, a mixed diet must be looked upon as the one for which our organisation is constructed, but I do not think it will be disputed that the capability exists of subsisting, and subsisting satisfactorily, upon a diet of animal food.

The idea to which I have just referred is exerting a prejudicial influence upon the treatment of diabetes by checking the fulness of dieting being carried out as in the interests of patients ought to be done. The progress of a case hinges upon a proper adjustment of the character of the food to the condition to be met; and, yet, do we not find, even in health resorts to which diabetics are specially sent for treatment, that although sugar may be present to a greater or less extent in the urine, food nominally, but nominally only, diabetic is ordered to be taken. In support of this statement I will simply mention, without naming the health resorts from which the food was derived, that, in the case of one, a specimen of the gluten bread that my patient had been ordered to take was found to contain in the water-free state 61·7, and, in the case of another, 73·7 per cent. of starch.

The employment of food of the kind just referred to, as a diabetic substitute for bread, simply constitutes an illusive representation of diabetic dieting. The effect may be regarded as tantamount to allowing the disease, as previous to the introduction of modern dieting, to take its own course, thereby putting time back fifty years. It is impossible for the disease to be satisfactorily treated without the necessary implements, in the form of proper food, and, in countries where this is not obtainable, nothing can be known about the beneficial results that are producible by the agency of its employment.

I have been speaking of the position held by food in connection with the treatment of diabetes. The effect produced is brought about by the removal of the abnormal state occasioned by the passage of sugar through the system. The fault to be dealt with is a defective assimilative power over carbohydrate, and what is wanted is a restoration of the missing power. In proportion as this is obtained, so will follow the capacity for taking carbohydrate, with the natural result of its passing to utilisation instead of traversing the system as sugar and running off in this form with the urine. Nothing can be more simple and intelligible than the matter that stands before us, and the view espoused with regard to it everywhere fits in with the facts presented. As long as there is the abnormal transit of sugar through the circulation going on a counteracting influence exists opposing the attainment of the object desired. Bring the condition of the system into a natural state and there is nothing to restrain the known tendency of Nature to rectify faults. It is in this way that dieting may be considered to act. It, indeed, performs a double *rôle*, viz. (1) that of getting rid of the toxic agent (sugar) which is exerting in every direction a damaging action upon the system, and (2) that of clearing the ground for the efforts of Nature to be afforded fair play.

The only drug agency as yet known that appears definitely to afford help in correcting the underlying state belonging to diabetes is that of opium and some of its derivatives. At present we have only empirical evidence to rest upon. From somewhat remote times, however, experience has afforded corroborative testimony in the direction of utility. In the Guy's Hospital *Reports* (3rd Series, vol. xv, 1870) I published a number of cases illustrating the influence of opium and some of its constituent principles in controlling the elimination of sugar in diabetes. Opium, morphia, and codeina were the agents from which affirmative results were found to be obtainable; and, of the three, I was led to consider that codeina, in view of all the circumstances, constituted the most advantageous for remedial employment in the disease. This opinion, I may say, my subsequent experience has confirmed.

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